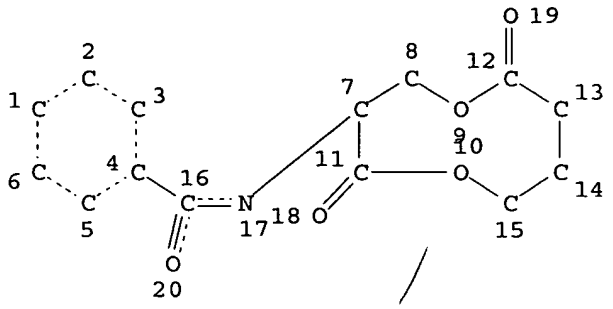
Owens
10/069431

=> d l3 que stat;fil hcapl;s l3
L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L3 129 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 528 ITERATIONS 129 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	163.05	163.26

FILE 'HCAPLUS' ENTERED AT 17:00:02 ON 25 MAR 2005
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FILE COVERS 1907 - 25 Mar 2005 VOL 142 ISS 14
FILE LAST UPDATED: 24 Mar 2005 (20050324/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L4 128 L3

Searched by: Mary Hale 571-272-2507 REM 1D86

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         97313 APOPTOS?
L5           3 L4 AND APOPTOS?

=> d 1-3 ibib abs hitstr
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Searched by: Mary Hale 571-272-2507 REM 1D86

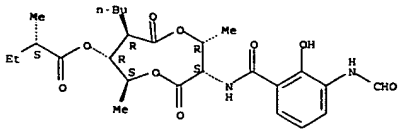
L5 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1000225 HCAPLUS
DOCUMENT NUMBER: 142:211698
TITLE: Acute changes in U937 nuclear Ca2+ preceding type 1 "apoptotic" programmed cell death to MK 886
AUTHOR(S): Anderson, K. M.; Rubenstein, M.; Alrefai, W. A.; Dudeja, P.; Tsui, P.; Harris, J. E.
CORPORATE SOURCE: Hektoen Institute, Department of Biochemistry, Rush University Medical Center, Chicago, IL, 60612, USA
SOURCE: Anticancer Research (2004), 24(5A), 2601-2615
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: MK 886, a 5-lipoxygenase inhibitor, induces a type 1 "apoptotic" form of programmed cell death in Bcl-2 pos. U937 monoblastoid cells. In Ca2+-depleted, nonpermeabilized U937 cells studied with MK 886 in a Ca2+-free medium, an acute increase in Ca2+ occurred within 10 to 20 s, detected with fura-2 measured with a spectrofluorimeter. Methods and Results: The increased fluorescence was nuclear in location, as judged by confocal microscopy. The antioxidant, N-acetyl-L-cysteine, three agents that inhibit mitochondrial function at identified sites, antimycin A, atractyloside and cyclosporin A, the L/N-channel inhibitor, loperamide and BAPTA, an intracellular Ca+ chelator preloaded into cells each reduced the extent or prevented the acute MK 886-induced rise in Ca2+, as determined by radiometric detection. Rhodamine-2, a more selective mitochondrial Ca2+ probe, provided no evidence for nuclear Ca2+ originating from that extra-nuclear site or from the endoplasmic reticulum. With 2',7'-dichloro-dihydrofluorescein-labeled cells to detect reactive oxygen species, MK 886 increased the initial fluorescent signal from a number of intracellular, largely extra-nuclear sites, including mitochondria. Two chems. that inhibit the function of Bcl-2, HA 14-1 and 2-methyl-antimycin A3, reduced the Ca2+ response to MK 886, if pre-incubated with the Bcl-2-pos. U937 cells at 37°C for several hours. MK 886 was previously shown to induce reactive oxygen species and a fall in mitochondrial membrane potential in both Bcl-2 pos. U937 and in Bcl-2-neg. PC-3 prostate and panc-1 pancreatic cancer cells. The latter solid tumor cells undergo an atypical "type 2" PCD without an acute rise in nuclear Ca2+. Conclusion: These results are consistent with an MK 886-induced increase of reactive oxygen species from intra-cellular sites including mitochondria which release Ca2+ located primarily at or near nuclei. These events may involve Bcl-2, participating in some form of Ca2+ channel and nuclear Ca2+ binding proteins undergoing conformational changes due to reactive oxygen species. Reasons for the different PCD responses in Bcl-2 pos. lympho-hematopoietic compared to Bcl-2-neg. solid cancer cell lines, resp. with and without the induced nuclear Ca2+ signal, remain to be defined.

IT **28068-14-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2-methylantimycin A3, Bcl-2 function inhibitor did not acutely alter rapid Ca2+ increase induced by MK 886 which induced rise in ROS from intra-cellular sites including mitochondria in human Bcl-2 pos. U937 monoblastoid cell)

L5 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RN 28068-14-6 HCAPLUS
CN Butanoic acid, 2-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:550994 HCAPLUS
DOCUMENT NUMBER: 139:122709
TITLE: Conjugates useful in the treatment of prostate cancer
INVENTOR(S): Defeo-Jones, Deborah; Jones, Raymond E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 70 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003133927	A1	20030717	US 2002-268552		20021010
PRIORITY APPLN. INFO.:			US 2001-328351P	P	20011010

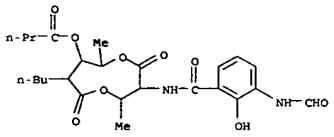
OTHER SOURCE(S): MARPAT 139:122709

AB Chemical conjugates which comprise an oligopeptide covalently bonded, either directly or through a chemical linker, to a peptide or small mol. that binds to an anti-apoptotic Bcl-2 family protein, inhibits the expression of the Bcl-2 family protein, or inhibits the function of the Bcl-2 family protein. Such a peptide or small mol. that binds to an anti-apoptotic Bcl-2 family protein, inhibits the expression of the Bcl-2 family protein, or inhibits the function of the Bcl-2 family protein may be conveniently referred to as a therapeutic agent. The oligopeptides are chosen from oligomers that are selectively recognized by the free prostate specific antigen (PSA) and are capable of being proteolytically cleaved by the enzymic activity of the free prostate specific antigen.

IT **522-70-3**, Antimycin a3 **642-15-9**, Antimycin A1
27220-60-6, Antimycin A5 **27220-61-7**, Antimycin A6
27414-07-9 **60504-95-2** **148163-08-0**,
Urauchimycin b **225939-28-6**, Kitamycin a **225939-29-7**,
Kitamycin b **561304-89-0D**, Antimycin A1a, conjugates
561304-90-3 **561304-91-4** **561304-93-6**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide conjugates useful in the treatment of prostate cancer)

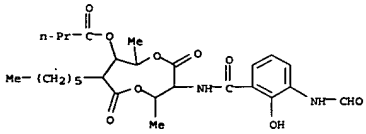
RN 522-70-3 HCAPLUS
CN Butanoic acid, 2(or 3)-methyl-, 3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester, (2R,3S,6S,7R,8R)- (9CI) (CA INDEX NAME)

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



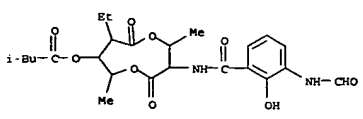
D1—Me

RN 642-15-9 HCAPLUS
CN Butanoic acid, 2(or 3)-methyl-, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)



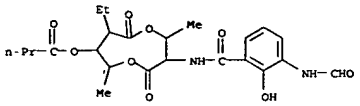
D1—Me

RN 27220-60-6 HCAPLUS
CN Butanoic acid, 3-methyl-, 8-ethyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

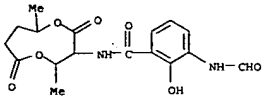


RN 27220-61-7 HCAPLUS
CN Butanoic acid, 8-ethyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

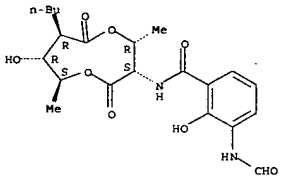


RN 27414-07-9 HCAPLUS
CN Benzamide, N-(2,6-dimethyl-4,9-dioxo-1,5-dioxonan-3-yl)-3-(formylamino)-2-hydroxy- (9CI) (CA INDEX NAME)



RN 60504-95-2 HCAPLUS
CN Benzamide, N-[(3S,4R,7R,8R,9S)-7-butyl-8-hydroxy-4,9-dimethyl-2,6-dioxo-1,5-dioxonan-3-yl]-3-(formylamino)-2-hydroxy- (9CI) (CA INDEX NAME)

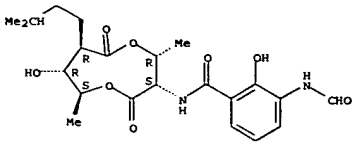
Absolute stereochemistry.



RN 148163-08-0 HCAPLUS
CN Benzamide, 3-(formylamino)-2-hydroxy-N-[(2R,3S,6S,7R,8R)-7-hydroxy-2,6-dimethyl-8-(3-methylbutyl)-4,9-dioxo-1,5-dioxonan-3-yl]- (9CI) (CA INDEX NAME)

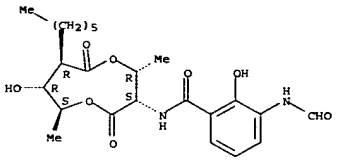
Absolute stereochemistry.

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



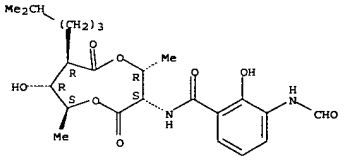
RN 225939-28-6 HCAPLUS
CN Benzamide, 3-(formylamino)-N-[(3S,4R,7R,8R,9S)-7-hexyl-8-hydroxy-4,9-dimethyl-2,6-dioxo-1,5-dioxonan-3-yl]-2-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 225939-29-7 HCAPLUS
CN Benzamide, 3-(formylamino)-2-hydroxy-N-[(2R,3S,6S,7R,8R)-7-hydroxy-2,6-dimethyl-8-(4-methylpentyl)-4,9-dioxo-1,5-dioxonan-3-yl]- (9CI) (CA INDEX NAME)

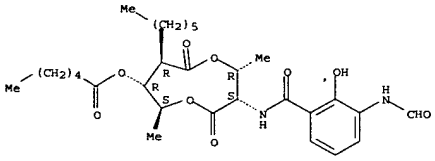
Absolute stereochemistry. Rotation (+).



RN 561304-89-0 HCAPLUS
CN Hexanoic acid, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

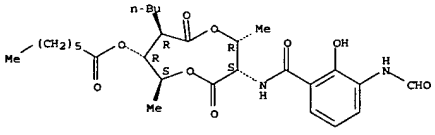
Absolute stereochemistry.

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



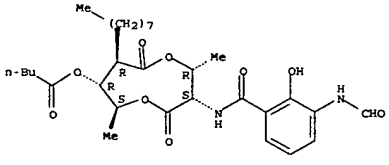
RN 561304-90-3 HCAPLUS
CN Heptanoic acid, (2R,3S,6S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 561304-91-4 HCAPLUS
CN Pentanoic acid, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-8-octyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

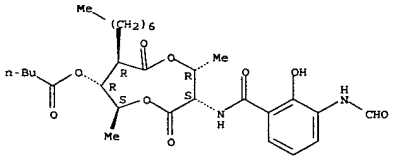
Absolute stereochemistry.



RN 561304-93-6 HCAPLUS
CN Pentanoic acid, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-heptyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



Searched by: Mary Hale 571-272-2507 REM 1D86

L5 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:152671 HCAPLUS
DOCUMENT NUMBER: 134:202680
TITLE: Compositions and methods using antimycin derivatives for modulating **apoptosis** in cells over-expressing Bcl-2 family member proteins
INVENTOR(S): Hockenbery, David M.; Simon, Julian A.; Tzung, Shie-Pon
PATENT ASSIGNEE(S): Fred Hutchinson Cancer Research Center, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001014365	A1	20010301	WO 2000-US22891	20000818
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2382465	AA	20010301	CA 2000-2382465	20000818
AU 2000070634	A5	20010319	AU 2000-70634	20000818
EP 1218368	A1	20020703	EP 2000-959287	20000818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003507474	T2	20030225	JP 2001-518696	20000818

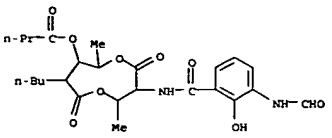
PRIORITY APPLN. INFO.: US 1999-149968P P 19990820
WO 2000-US22891 W 20000818

OTHER SOURCE(S): MARPAT 134:202680

AB Agents and compns. are provided for modulating the apoptotic state of a cell. The agents comprise derivs. of antimycins which bind to an anti-apoptotic Bcl-2 family member protein. Further, the agents preferentially induce **apoptosis** in cells that over-express anti-apoptotic Bcl-2 family member proteins and typically exhibit reduced binding affinity for cytochrome B. Pharmaceutical uses of the agents and compns. include treating **apoptosis**-associated disease, such as neoplasia and drug resistance, are also disclosed.

IT **522-70-3**, Antimycin A3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(antimycin derivs. for modulating **apoptosis** in cells over-expressing Bcl-2 family member proteins)

RN 522-70-3 HCAPLUS
CN Butanoic acid, 2(or 3)-methyl-, 3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester, (2R,3S,6S,7R,8R)- (9CI) (CA INDEX NAME)

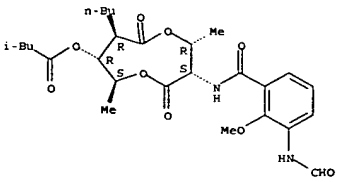


D1—Me

IT **118890-43-0P 327993-52-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antimycin derivs. for modulating **apoptosis** in cells over-expressing Bcl-2 family member proteins)

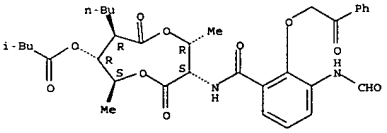
RN 118890-43-0 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-methoxybenzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



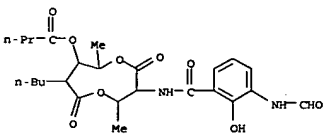
RN 327993-52-2 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-(2-oxo-2-phenylethoxy)benzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



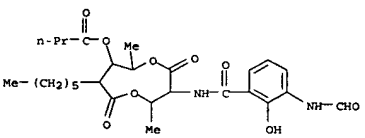
IT **522-70-3D**, Antimycin A3, derivs. **642-15-9D**, Antimycin A1, derivs. **21788-41-0 21788-42-1 116095-17-1 132864-77-8 132956-88-8 327993-44-2 327993-45-3 327993-46-4 327993-47-5 327993-48-6 327993-49-7 327993-50-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimycin derivs. for modulating **apoptosis** in cells over-expressing Bcl-2 family member proteins)

RN 522-70-3 HCAPLUS
CN Butanoic acid, 2(or 3)-methyl-, 3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester, (2R,3S,6S,7R,8R)- (9CI) (CA INDEX NAME)



D1—Me

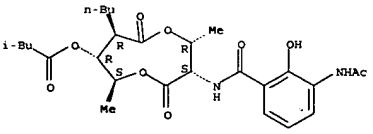
RN 642-15-9 HCAPLUS
CN Butanoic acid, 2(or 3)-methyl-, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)



D1—Me

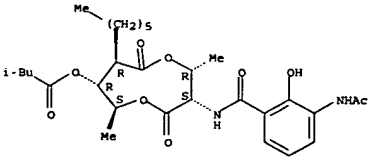
RN 21788-41-0 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-3-[[3-(acetylamino)-2-hydroxybenzoyl]amino]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 21788-42-1 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-3-[[3-(acetylamino)-2-hydroxybenzoyl]amino]-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

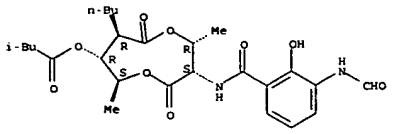
Absolute stereochemistry.



RN 116095-17-1 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6-dimethyl-9-oxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

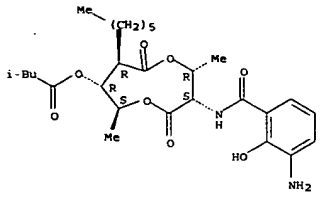
Searched by: Mary Hale 571-272-2507 REM 1D86

Absolute stereochemistry.



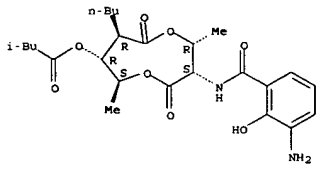
RN 132864-77-8 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-3-[(3-amino-2-hydroxybenzoyl)amino]-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 132956-88-8 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-3-[(3-amino-2-hydroxybenzoyl)amino]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

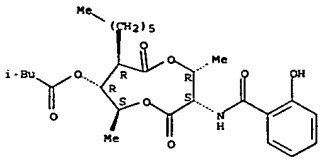
Absolute stereochemistry.



RN 327993-44-2 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-hexyl-3-[(2-

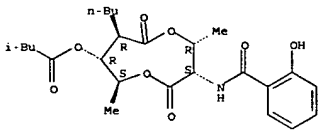
hydroxybenzoyl)amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



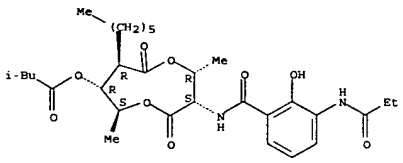
RN 327993-45-3 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[(2-hydroxybenzoyl)amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 327993-46-4 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-hexyl-3-[[2-hydroxy-3-[(1-oxopropyl)amino]benzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

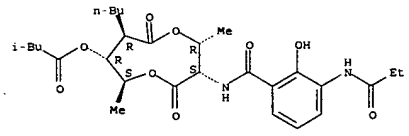
Absolute stereochemistry.



RN 327993-47-5 HCAPLUS

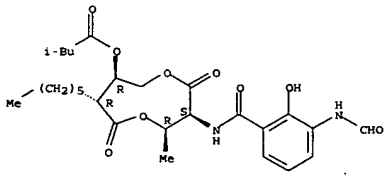
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-8-butyl-3-[[2-hydroxy-3-[(1-oxopropyl)amino]benzoyl]amino]-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



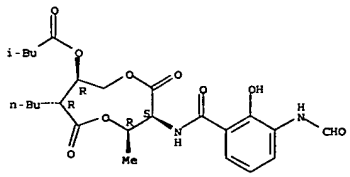
RN 327993-48-6 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,7R,8R)-3-[(3-(formylamino)-2-hydroxybenzoyl]amino]-8-hexyl-2-methyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



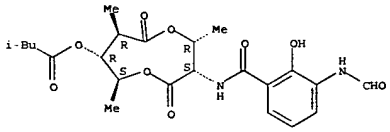
RN 327993-49-7 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,7R,8R)-8-butyl-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2-methyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 327993-50-0 HCAPLUS
CN Butanoic acid, 3-methyl-, (2R,3S,6S,7R,8R)-3-[[3-(formylamino)-2-hydroxybenzoyl]amino]-2,6,8-trimethyl-4,9-dioxo-1,5-dioxonan-7-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by: Mary Hale 571-272-2507 REM 1D86

```
=> s l4 not l5
L6          125 L4 NOT L5

=> s l6 and (hockenberry d?/au or simon j?/au;s tzung s?/au
UNMATCHED LEFT PARENTHESIS 'AND (HOCKENBERR'
COMMAND STACK INTERRUPTED.  ENTER "DISPLAY HISTORY"
TO SEE WHICH COMMANDS WERE EXECUTED.

The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l6 and (hockenberry d?/au or simon j?/au;s tzung s?/au)
UNMATCHED LEFT PARENTHESIS 'AND (HOCKENBERR'
COMMAND STACK INTERRUPTED.  ENTER "DISPLAY HISTORY"
TO SEE WHICH COMMANDS WERE EXECUTED.

The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l6 and (hockenberry d?/au or simon j?/au or s tzung s?/au)
             3 HOCKENBERRY D?/AU
          2232 SIMON J?/AU
             0 S TZUNG S?/AU
L7           1 L6 AND (HOCKENBERRY D?/AU OR SIMON J?/AU OR S TZUNG S?/AU)

=> d
```

Searched by: Mary Hale 571-272-2507 REM 1D86

L7 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:126529 HCAPLUS
DN 134:336053
TI Antimycin A mimics a cell-death-inducing Bcl-2 homology domain 3
AU Tzung, Shie-Pon; Kim, Kristine M.; Basanez, Gorka; Giedt, Chris D.; Simon, Julian; Zimmerberg, Joshua; Zhang, Kam Y. J.; Hockenbery, David M.
CS Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, WA, 98195, USA
SO Nature Cell Biology (2001), 3(2), 183-192
CODEN: NCBIFN; ISSN: 1465-7392
PB Nature Publishing Group
DT Journal
LA English
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by: Mary Hale 571-272-2507 REM 1D86

```
=> s l3 and (bcl2 or bcl 2 or bcl xl or bh1 or bh2 or bh3)
           128 L3
          6972 BCL2
         19431 BCL
            19 BCLS
         19438 BCL
                 (BCL OR BCLS)
       8331410 2
         16571 BCL 2
                 (BCL(W)2)
         19431 BCL
            19 BCLS
         19438 BCL
                 (BCL OR BCLS)
          8187 XL
            95 XLS
          8278 XL
                 (XL OR XLS)
          3691 BCL XL
                 (BCL(W)XL)
           165 BH1
          1187 BH2
          4543 BH3
L8           4 L3 AND (BCL2 OR BCL 2 OR BCL XL OR BH1 OR BH2 OR BH3)

=> s l8 not (l4 or l5 or l7)
L9           0 L8 NOT (L4 OR L5 OR L7)

=> fil medl,biosis,embase;s l4
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    28.17     191.43

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -2.19      -2.19

FILE 'MEDLINE' ENTERED AT 17:02:59 ON 25 MAR 2005

FILE 'BIOSIS' ENTERED AT 17:02:59 ON 25 MAR 2005
Copyright (c) 2005 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 17:02:59 ON 25 MAR 2005
COPYRIGHT (C) 2005 Elsevier Inc. All rights reserved.


L10       2376 FILE MEDLINE
L11         15 FILE BIOSIS
L12       1357 FILE EMBASE

TOTAL FOR ALL FILES
L13       3748 L4

=> s l13 and apoptos?
L14         60 FILE MEDLINE
L15          0 FILE BIOSIS
L16         87 FILE EMBASE

TOTAL FOR ALL FILES



Searched by: Mary Hale 571-272-2507 REM 1D86
```

```
L17         147 L13 AND APOPTOS?

=> s l17 and (bcl2 or bcl 2 or bcl or bh1 or bh2 or bh3)
L18          15 FILE MEDLINE
L19           0 FILE BIOSIS
L20          39 FILE EMBASE

TOTAL FOR ALL FILES
L21          54 L17 AND (BCL2 OR BCL 2 OR BCL OR BH1 OR BH2 OR BH3)

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22           47 DUP REM L21 (7 DUPLICATES REMOVED)

=> d 1-47 ibib abs
```

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 1 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004453571 EMBASE
TITLE: Acute changes in U937 nuclear Ca(2+) preceding type 1 "apoptotic" programmed cell death due to MK 886.
AUTHOR: Anderson K.M.; Rubenstein M.; Alrefai W.A.; Dudeja P.; Tsui P.; Harris J.E.
CORPORATE SOURCE: Dr. K.M. Anderson, c/o Dr. Marvin Rubenstein, Hektoen Institute, 2100 W Harrison, Chicago, IL 60612, United States. marander427@MSN.com
SOURCE: Anticancer Research, (2004) 24/5 A (2601-2615). Refs: 76 ISSN: 0250-7005 CODEN: ANTRD4
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: MK 886, a 5-lipoxygenase inhibitor, induces a type 1 "apoptotic" form of programmed cell death in **Bcl-2** -positive U937 monoblastoid cells. In Ca(2+)-depleted, non-permeabilized U937 cells studied with MK 886 in a Ca(2+)-free medium, an acute increase in Ca(2+) occured within 10 to 20 seconds, detected with fura-2 measured with a spectrofluorimeter. Methods and Results: The increased fluorescence was nuclear in location, as judged by confocal microscopy. The antioxidant, N-acetyl-L-cysteine, three agents that inhibit mitochondrial function at identified sites, antimycin A, atractyloside and cyclosporin A, the L/N-channel inhibitor, loperamide and BAPTA, an intracellular Ca(+) chelator pre-loaded i nto cells each reduced the extent or prevented the acute MK 886-induced rise in Ca(2+), as determined by radiometric detection. Rhodamine-2, a more selective mitochondria! Ca(2+) probe, provided no evidence for nuclear Ca(2+) originating from that extra-nuclear site or from the endoplasmic reticulum. With 2', 7'-dichloro- dihydrofluorescein-labelled cells to detect reactive oxygen species, MK 886 increased the initial fluorescent signal from a number of intracellular, largely extra-nuclear sites, including mitochondria. Two chemicals that inhibit the function of **Bcl-2**, HA14-1 and 2-methyl-antimycin A3, reduced the Ca(2+) response to MK 886, if pre-incubated with the **Bcl-2**-positive U937 cells at 37°C for several hours. MK 886 was previously shown to induce reactive oxygen species and a fall in mitochondrial membrane potential in both **Bcl-2**-positive U937 and in **Bcl-2**-negative PC-3 prostate and panc-1 pancreatic cancer cells. The latter solid tumor cells undergo an atypical "type 2" PCD without an acute rise in nuclear Ca(2+). Conclusion: These results are consistent with an MK 886-induced increase of reactive oxygen species from intra-cellular sites including mitochondria which release Ca (2+) located primarily at or near nuclei. These events may involve **Bcl-2**, participating in some form of Ca(2+) channel and nuclear Ca (2+) binding proteins undergoing conformational changes due to reactive oxygen species. Reasons for the different PCD responses in **Bcl-2** positive lympho-hematopoietic compared to **Bcl-2**

L22 ANSWER 1 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. (Continued)
-negative solid cancer cell lines, respectively with and without the induced nuclear Ca(2+) signal, remain to be defined.

L22 ANSWER 2 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004030793 EMBASE
TITLE: **Bcl-X(L)** Mutations Suppress Cellular Sensitivity to Antimycin A.
AUTHOR: Manion M.K.; O'Neill J.W.; Giedt C.D.; Kim K.M.; Zhang K.Y.Z.; Hockenbery D.M.
CORPORATE SOURCE: D.M. Hockenbery, Division of Human Biology, Clinical Research, Fred Hutchinson Cancer Res. Center, Seattle, WA 98109, United States. dhockenb@fhcrc.org
SOURCE: Journal of Biological Chemistry, (16 Jan 2004) 279/3 (2159-2165). Refs: 25 ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cells expressing high levels of the **BCL-X(L)** anti-apoptotic protein are preferentially killed by the mitochondrial inhibitor antimycin A (AA). Computational modeling predicts a binding site for AA in the extended hydrophobic groove on **BCL-X(L)**, previously identified as an interface for dimerization to BAX and related pro-apoptotic proteins. Here, we identify **BCL-X(L)** hydrophobic groove mutants with normal cellular anti-apoptotic function but suppressed sensitivity to AA. The LD(50) of AA for cells expressing **BCL-X(L)** mutants directly correlates with the measured in vitro dissociation constants for AA binding. These results indicate that **BCL-X(L)** is a principal target mediating AA cytotoxicity.

L22 ANSWER 3 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004149210 EMBASE
TITLE: Current strategies to target the anti-apoptotic **Bcl-2** protein in cancer cells.
AUTHOR: Oxford S.M.E.; Dallman C.L.; Johnson P.W.M.; Ganesan A.; Packham G.
CORPORATE SOURCE: G. Packham, Cancer Research UK Oncology Unit, Southampton General Hospital, The Somers Cancer Sciences Building, Southampton SO16 6YD, United Kingdom. G.K.Packham@soton.ac.uk
SOURCE: Current Medicinal Chemistry, (2004) 11/8 (1031-1040). Refs: 95 ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Apoptosis** (or programmed cell death) is a genetically controlled "cell suicide" pathway which plays an essential role in deleting excess, unwanted or damaged cells during development and tissue homeostasis. Dysregulation of **apoptosis** contributes to a wide variety of pathological conditions, including AIDS, cardiovascular disease, infectious disease, autoimmunity and neurodegenerative disorders. Resistance to **apoptosis** is also a common feature in human malignancies, contributing to both the development of cancer and resistance to conventional therapies such as radiation and cytotoxic drugs, which function by activating apoptotic cell death pathways. **Bcl-2** is one of the best characterized cell death control proteins; its overexpression confers resistance to a broad range of **apoptosis** inducers and the cell survival functions of **Bcl-2** are activated by translocation in lymphomas and overexpression in many other cancer types. A wealth of experimental data supports the idea that **Bcl-2** is an attractive and tractable target for newer molecularly directed anti-cancer strategies, designed to promote cancer cell death. Here we review current understanding of the mechanism of action and importance of **Bcl-2** in cancer cells and progress in developing new agents to target this key survival molecule. .COPYRGT. 2004 Bentham Science Publishers Ltd.

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L22 ANSWER 4 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004285865 EMBASE
TITLE: Bcl-2-targeted cancer therapeutics.
AUTHOR: Khorchid A.; Beauparlant P.
CORPORATE SOURCE: P. Beauparlant, Gemin X Biotechnologies Inc., 3576 Avenue du Parc, Montreal, Que. H2X 2H7, Canada. pbeauparlant@geminx.com
SOURCE: Expert Opinion on Therapeutic Patents, (2004) 14/6 (805-818).
Refs: 99
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The antiapoptotic members of the Bcl-2 family of proteins play multiple roles in cancer. These membrane-integrated proteins inhibit the pro-apoptotic activity of oncogenes during oncogenesis, support the survival of established cancer cells, and increase resistance to chemotherapy. Hence, strategies aimed at inhibiting the expression or activity of Bcl-2 proteins are predicted to have therapeutic value. Several antisense oligonucleotides (AO), capable of reducing expression of either Bcl-2 or Bcl -X(L), were shown to induce apoptosis in cancer cells, to inhibit tumour growth in certain mouse tumour models, and to sensitise cancer cells to chemotherapy. One such AO, oblimersen, is presently being evaluated in combination with standard therapy in patients with advanced cancers, including chronic lymphocytic leukaemia and multiple myeloma. Bcl-2 proteins are thought to inhibit apoptosis by interacting with the pro-apoptotic proteins Bax and Bak, and preventing their activation. Small molecules capable of inhibiting this interaction have been discovered and shown to induce apoptosis in cancer cells. Gossypol and chelerythrine are two such molecules that inhibit tumour growth in mouse tumour models. This review summarises the evidence supporting the role of Bcl-2 proteins in cancer and then examines patented therapeutic strategies that target Bcl-2 protein expression or activities. 2004 .COPYRGT. Ashley Publications Ltd.

L22 ANSWER 5 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2004315833 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15218549
TITLE: Inhibition of mitochondrial bioenergetics: the effects on structure of mitochondria in the cell and on apoptosis.
AUTHOR: Lyamzaev Konstantin G; Izyumov Denis S; Avetisyan Armine V; Yang Fuyu; Pletjushkina Olga Yu; Chernyak Boris V
CORPORATE SOURCE: A.N. Belozersky Institute of Physico-Chemical Biology, Moscow State University, Moscow, Russia.
SOURCE: Acta biochimica Polonica, (2004) 51 (2) 553-62.
Journal code: 14520300R. ISSN: 0001-527X.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 20040626
Last Updated on STN: 20050301
Entered Medline: 20050225
AB The effects of specific inhibitors of respiratory chain, F(o)F(1)ATP synthase and uncouplers of oxidative phosphorylation on survival of carcinoma HeLa cells and on the structure of mitochondria in the cells were studied. The inhibitors of respiration (piericidin, antimycin, myxothiazol), the F(1)-component of ATP synthase (aurovertin) and uncouplers (DNP, FCCP) did not affect viability of HeLa cells, apoptosis induced by TNF or staurosporin and the anti-apoptotic action of Bcl-2. Apoptosis was induced by combined action of respiratory inhibitors and uncouplers indicating possible pro-apoptotic action of reactive oxygen species (ROS) generated by mitochondria. Short-term incubation of HeLa cells with the mitochondrial inhibitors and 2-deoxyglucose followed by 24-48 h recovery resulted in massive apoptosis. Apoptosis correlated to transient (3-4 h) and limited (60-70%) depletion of ATP. More prolonged or more complete transient ATP depletion induced pronounced necrosis. The inhibitors of respiration and uncouplers caused fragmentation of tubular mitochondria and formation of small round bodies followed by swelling. These transitions were not accompanied with release of cytochrome c into the cytosol and were fully reversible. The combined effect of respiratory inhibitors and uncouplers developed more rapidly indicating possible involvement of ROS generated by mitochondria. More prolonged (48-72 h) incubation with this combination of inhibitors caused clustering and degradation of mitochondria.

L22 ANSWER 6 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004243435 EMBASE
TITLE: Small-molecule inhibitors of Bcl-2 protein.
AUTHOR: Pulley H.; Mohammad R.
CORPORATE SOURCE: R. Mohammad, Division of Hematology and Oncology, Dept. Int. Med./Karmanos Cancer I., Wayne State Univ. School of Medicine, 724 HWCRC 4100 John R St., Detroit, MI 48201, United States. Mohammad@karmanos.org
SOURCE: Drugs of the Future, (2004) 29/4 (369-381).
Refs: 75
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Approaches to drug discovery are varied and range from high-resolution NMR solution structure of targeted molecules to rational design. This review is focused on the use of small-molecule inhibitors of Bcl-2 as therapeutic agents. Members of the Bcl-2 family of proteins are crucial regulators of apoptotic cell death. Human cancers have been found to overexpress Bcl-2 and Bcl-XL. Cells with high levels of these antiapoptotic molecules are usually resistant to a wide spectrum of chemotherapeutic drugs. Targeting the Bcl-2 family of proteins with small-molecule inhibitors has therefore become an attractive potential therapy for a variety of cancers. The role of Bcl-2 in sabotaging the success of cytotoxic agents suggests that novel treatments should be devised to target Bcl-2-overexpressing tumor cells and induce apoptosis directly. In this article, we will provide a review of potential small-molecule inhibitors as anticancer agents. The deregulated overexpression of Bcl-2 and Bcl-XL is directly related to cancer cell survival and resistance to chemotherapeutic drugs, making antagonists or inhibitors of these proteins very promising candidates for use in cancer therapy.

L22 ANSWER 7 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2005025194 EMBASE
TITLE: Deregulation of catalase, not MnSOD, is associated with necrotic death of p53-defective DF-1 cells under antimycin A-induced oxidative stress.
AUTHOR: You S.; Kong B.-W.; Jeon S.-Y.; Foster D.N.; Kim H.
CORPORATE SOURCE: S. You, Lab. of Cell Growth/Function Regul., Coll. of Life/Environmental Sciences, Korea University, Seoul 136-701, United States. bioseung@korea.ac.kr
SOURCE: Molecules and Cells, (31 Oct 2004) 18/2 (220-229).
Refs: 39
ISSN: 1016-8478 CODEN: MOCEEK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB One of distinct genetic alterations in spontaneously immortalized DF-1 cells was found to be dysfunction of p53 and E2F-1 as well as altered antioxidant gene expression (upregulation of MnSOD and downregulation of catalase). We have characterized the cellular responses of primary and immortal DF-1 cells to oxidative stress and found that DF-1 cells were more sensitive to oxidative stress than their primary counterparts when treated with antimycin A. The increased DF-1 cell death by oxidative stress was accompanied by an increase in the levels of intracellular superoxide anions and hydrogen peroxide. The cell death in DF-1 cells by antimycin A showed none of the hallmarks of apoptosis, but displayed a significantly increased necrotic cell population. Anti-apoptotic Bcl-2 failed to inhibit oxidative-induced necrotic cell death in the DF-1 cells. However, this necrotic cell death was significantly decreased by treatment with hydrogen peroxide scavengers such as sodium pyruvate and N-acetyl-cysteine. Interestingly, overexpression of human catalase in DF-1 cells endowed cells resistant to the oxidative stress by antimycin A treatment, although the downregulation of MnSOD by an antisense strategy showed no evident change in the cytotoxic effect caused by antimycin A. Taken together, the present study might provide new therapeutic approach for tumor cells having the loss of p53 function and the altered antioxidant functions. .COPYRGT. KSMCB 2004.

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L22 ANSWER 8 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004224187 EMBASE
TITLE: **Apoptosis** shifts to necrosis via intermediate types of cell death by a mechanism depending on c-myc and **bcl-2** expression.
AUTHOR: Papucci L.; Formigli L.; Schiavone N.; Tani A.; Donnini M.;
Lapucci A.; Perna F.; Tempestini A.; Witort E.; Morganti M.; Nosi D.; Orlandini G.E.; Orlandini S.Z.; Capaccioli S.
CORPORATE SOURCE: S. Capaccioli, Dept. of Exp. Pathology and Oncology, University of Florence, Via le Morgagni 50, 50132 Florence,
Italy. sergio@unifi.it
SOURCE: Cell and Tissue Research, (2004) 316/2 (197-209).
Refs: 74
ISSN: 0302-766X CODEN: CTSRCS
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hypoxic and chemical hypoxia (antimycin A) commits cultured rat fibroblasts (Rat-1) towards **apoptosis**, necrosis or an intermediate form of cell death (aponecrosis) depending on the degree of hypoxia. Aponecrosis also occurs in vivo. Here, we demonstrate that c-myc and **bcl-2**, two proto-oncogenes known to lower or to enhance, respectively, the apoptotic threshold, also affect the type of cell death: **apoptosis** shifts to aponecrosis and aponecrosis to necrosis, depending on c-myc or **bcl-2** expression and the antimycin A concentration (100-400 μM). In cells with basal gene expression, **apoptosis** shifts to aponecrosis/necrosis at 300 μM antimycin A (middle hypoxia). Overexpression of c-myc markedly increases cumulative cell death in response to antimycin A and lowers the antimycin A concentration required to shift **apoptosis** to aponecrosis/necrosis from 300 μM to 100 μM (low hypoxia). Overexpression of **bcl-2** elicits the opposite effect, decreasing cumulative cell death in response to antimycin A and raising the drug concentration required to shift **apoptosis** to aponecrosis/necrosis to 400 μM (high hypoxia). The passage from one to the other form of cell death involves various aponecrotic features with observed intermediate aspects between **apoptosis** and necrosis, a progressive increase in necrotic features being correlated with an increase in antimycin A concentration. The mechanism underlying the various effects of c-myc and **bcl-2** on cell-death type has been related to the ability of these genes to counteract, to various extents, the ATP decrease occurring in response to different degrees of chemical hypoxia. .COPYRGT. Springer-Verlag 2004.

L22 ANSWER 9 OF 47 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004117037 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15007303
TITLE: Oligomycin and antimycin A prevent nitric oxide-induced **apoptosis** by blocking cytochrome C leakage.
AUTHOR: Dairaku Naohiro; Kato Katsuaki; Honda Kennichi; Koike Tomoyuki; Iijima Katsunori; Imatani Akira; Sekine Hitoshi; Ohara Shuichi; Matsui Hiroshi; Shimosegawa Tooru
CORPORATE SOURCE: Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.
SOURCE: Journal of laboratory and clinical medicine, (2004 Mar) 143
(3) 143-51.
Journal code: 0375375. ISSN: 0022-2143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040310
Last Updated on STN: 20040423
Entered Medline: 20040422
AB Nitric oxide (NO) is a potent inducer of **apoptosis**, and its cytotoxicity is closely related to mitochondrial dysfunction. In this study we investigated the effects of a F0F1-ATPase inhibitor, oligomycin, and a mitochondrial respiratory chain complex III inhibitor, antimycin A, on NO-induced **apoptosis**. We used a normal rat gastric-epithelium cell line, RGM-1, treated with a pure NO donor, NOC-1 -1-hydroxy-2-oxo-3,3-bis(2-aminoethyl)-1-triazene - in the presence or absence of oligomycin or antimycin A. Changes in the expressions of Bax or **Bcl-2** proteins, release of cytochrome C from mitochondria into the cytosol, activation of caspase-3, and changes in the mitochondrial membrane potential (DeltaPsi) were measured with the use of Western blotting, c43 lorimetric assays, and a mitochondrial potential sensor, JC-1 dye. Treatment with NOC-18 induced dose-dependent apoptotic cell death in RGM-1 cells. Cell death was accompanied by mitochondrial depolarization, increases in Bax protein expression and cytochrome C leakage, and, subsequently, caspase-3 activation. Oligomycin and antimycin A prevented NO-induced **apoptosis** in a dose-dependent fashion by preventing cytochrome C release independent of **Bcl-2** expression. However, neither compound affected the up-regulation of Bax protein. On the one hand, oligomycin treatment was not accompanied by a decline in DeltaPsi. On the other hand, antimycin A treatment decreased DeltaPsi regardless of NOC-18 treatment. The findings of this study suggest that various functional molecules that constitute the mitochondrial respiratory chain may contribute to cytochrome C release that occurs during NO-induced **apoptosis**.

L22 ANSWER 10 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004520735 EMBASE
TITLE: Promises and challenges of targeting **Bcl-2** anti-apoptotic proteins for cancer therapy.
AUTHOR: O'Neill J.; Manion M.; Schwartz P.; Hockenbery D.M.
CORPORATE SOURCE: . dhockenb@fred.fhcrc.org
SOURCE: Biochimica et Biophysica Acta - Reviews on Cancer, (10 Dec 2004) 1705/1 (43-51).
Refs: 61
ISSN: 0304-419X CODEN: BBACEU
PUBLISHER IDENT.: S 0304-419X(04)00060-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cancer cells with elevated levels of **BCL-2** and related survival proteins are broadly resistant to cytotoxic agents. Antisense oligodeoxynucleotides, and more recently small molecule ligands for **BCL-2** and **BCL-X(L)**, are directly cytotoxic or synergistic with standard cytotoxic agents, and in some cases, may demonstrate selectivity for tumor cells. The usual issues for rational drug discovery are writ large upon **BCL-2**-targeted therapeutics. The molecular functions of **BCL-2** are not well understood, such that validation of cytotoxic mechanisms related to **BCL-2** as well as identification of surrogate markers for **BCL-2** function are significant obstacles for drug development. Despite these problems, a substantial number of small molecules that bind to **BCL-2** or **BCL-X(L)** are now available for pre-clinical testing; in turn, basic studies with these reagents should yield new insights about optimal strategies to disrupt **BCL-2** survival functions. .COPYRGT. 2004 Elsevier B.V. All rights reserved.

L22 ANSWER 11 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003517898 EMBASE
TITLE: Reactive Oxygen Species Generation and Mitochondrial Dysfunction in the Apoptotic Response to Bortezomib, a Novel Proteasome Inhibitor, in Human H460 Non-small Cell Lung Cancer Cells.
AUTHOR: Ling Y.-H.; Liebes L.; Zou Y.; Perez-Soler R.
CORPORATE SOURCE: Y.-H. Ling, Dept. of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, United States. yling@aecom.yu.edu
SOURCE: Journal of Biological Chemistry, (5 Sep 2003) 278/36 (33714-33723).
Refs: 57
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Bortezomib, a proteasome inhibitor, shows substantial anti-tumor activity in a variety of tumor cell lines, is in phase I, II, and III clinical trials and has recently been approved for the treatment of patients with multiple myeloma. The sequence of events leading to **apoptosis** following proteasome inhibition by bortezomib is unclear. Bortezomib effects on components of the mitochondrial apoptotic pathway were examined: generation of reactive oxygen species (ROS), alteration in the mitochondrial membrane potential ($\Delta\psi(m)$), and release of cytochrome c from mitochondria. With human H460 lung cancer cells, bortezomib exposure at 0.1 MM showed induction of apoptotic cell death starting at 24 h, with increasing effects after 48-72 h of treatment. After 3-6 h, an elevation in ROS generation, an increase in $\Delta\psi(m)$, and the release of cytochrome c into the cytosol, were observed in a time-dependent manner. Co-incubation with rotenone and antimycin A, inhibitors of mitochondrial electron transport chain complexes I and III, or with cyclosporine A, an inhibitor of mitochondrial permeability transition pore, resulted in inhibition of bortezomib-induced ROS generation, increase in $\Delta\psi(m)$, and cytochrome c release. Tiron, an antioxidant agent, blocked the bortezomib-induced ROS production, $\Delta\psi(m)$ increase, and cytochrome c release. Tiron treatment also protected against the bortezomib-induced PARP protein cleavage and cell death. Benzyloxycarbonyl-VAD-fluoromethyl ketone, an inhibitor of pan-caspase, did not alter the bortezomib-induced ROS generation and increase in $\Delta\psi(m)$, although it prevented bortezomib-induced poly(ADP-ribose) polymerase cleavage and apoptotic death. In PC-3 prostate carcinoma cells (with overexpression of **Bcl-2**), a reduction of bortezomib-induced ROS generation, $\Delta\psi(m)$ increase was correlated with cellular resistance to bortezomib and the attenuation of drug-induced **apoptosis**. The transient transfection of wild type p53 in p53 null H358 cells caused stimulation of the bortezomib-induced **apoptosis** but failed to enhance ROS generation and $\Delta\psi(m)$ increase. Thus ROS generation plays a critical role in the initiation of the bortezomib-induced apoptotic cascade by mediation of the disruption of $\Delta\psi(m)$ and the release of cytochrome c from mitochondria.

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L22 ANSWER 12 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003495111 EMBASE
TITLE: Strategies for reversing drug resistance.
AUTHOR: Fojo T.; Bates S.
CORPORATE SOURCE: T. Fojo, Center for Cancer Research, National Cancer Institute, Building 10, 9000 Rockville Pike, Bethesda, MA 20892, United States. tfojo@helix.nih.gov
SOURCE: Oncogene, (20 Oct 2003) 22/47 REV. ISS. 6 (7512-7523). Refs: 141
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Drug resistance, intrinsic or acquired, is a problem for all chemotherapeutic agents. In this review, we examine numerous strategies that have been tested or proposed to reverse drug resistance. Included among these strategies are approaches targeting the **apoptosis** pathway. Although the process of **apoptosis** is complex, it provides several potential sites for therapeutic intervention. A variety of targets and approaches are being pursued, including the suppression of proteins inhibiting **apoptosis** using antisense oligonucleotides (ASOs), and small molecules targeted at proteins that modulate **apoptosis**. An alternate strategy is based on numerous studies that have documented methylation of critical regions in the genome in human cancers. Consequently, efforts have been directed at re-expressing genes, including genes that affect drug sensitivity, using 5-azacytidine and 2'-deoxy-5- azacytidine (DAC, decitabine) as demethylating agents. While this strategy may be effective as a single modality, success will most likely be achieved if it is used to modulate gene expression in combination with other modalities such as chemotherapy. At a more basic level, attempts have been made to modulate glutathione (GSH) levels. Owing to its reactivity and high intracellular concentrations, GSH has been implicated in resistance to several chemotherapeutic agents. Several approaches designed to deplete intracellular GSH levels have been pursued including the use of buthionine-(S,R)-sulfoxime (BSO), a potent and specific inhibitor of γ-glutamyl cysteine synthetase (γ-GCS), the rate-limiting step in the synthesis of GSH, a hammerhead ribozyme against γ-GCS mRNA to downregulate specifically its levels and targeting cJun expression to reduce GSH levels. Alternate strategies have targeted p53. The frequent occurrence of p53 mutations in human cancer has led to the development of numerous approaches to restore wild-type (wt) p53. The goals of these interventions are to either revert the malignant phenotype or enhance drug sensitivity. The approach most extensively investigated has utilized one of several viral vectors. An alternate approach, the use of small molecules to restore wt function to mutant p53, remains an option. Finally, the conceptually simplest mechanism of resistance is one that reduces intracellular drug accumulation. Such reduction can be effected by a variety of drug efflux pumps, of which the most widely studied is P-glycoprotein (Pgp). The first strategy utilized to inhibit Pgp function relied on the identification of

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nonchemotherapeutic agents as competitors. Other approaches have included the use of hammerhead ribozymes against the MDR-1 gene and MDR-1-targeted ASOs. Although modulation of drug resistance has not yet been proven to be an effective clinical tool, we have learned an enormous amount about drug resistance. Should we succeed, these pioneering basic and clinical studies will have paved the road for future developments.

L22 ANSWER 13 OF 47 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003338929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12871126
TITLE: **Bcl-2**-related proteins as drug targets.
AUTHOR: O'Neill Jason W; Hockenbery David M
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
SOURCE: Current medicinal chemistry, (2003 Aug) 10 (16) 1553-62. Ref: 96
Journal code: 9440157. ISSN: 0929-8673.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030722
Last Updated on STN: 20031218
Entered Medline: 20031118

AB The **Bcl-2** family of proteins provide the most unambiguous link between mitochondrial functions and **apoptosis**, as their only (or principal) functions appear to be as regulators of this cell death pathway. Rational drug design to manipulate the functions of these proteins has been hampered by the lack of a clear understanding of a biochemical or molecular function, with disruption of intra-family protein-protein interactions as the only known, but daunting, objective. There has been substantial progress in this task using molecular modeling and drug leads. The prospects are also good for development of chemical tools for functional analysis of the **Bcl-2** proteins.

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 14 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003330473 EMBASE
TITLE: Recent advances in the development of anticancer agents targeting cell death inhibitors in the Bcl-2 protein family.
AUTHOR: Shangary S.; Johnson D.E.
CORPORATE SOURCE: Dr. S. Shangary, Division of Hematology/Oncology, Univ. of Pittsburgh Cancer Institute, Hillman Cancer Ctr. Res. Pavillion, 5117 Centre Avenue, Pittsburg, PA 15213-1863, United States
SOURCE: Leukemia, (1 Aug 2003) 17/8 (1470-1481).
Refs: 182
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Hematopoietic malignancies frequently are characterized by defects in apoptosis signaling. This renders the malignant cells resistant to endogenous apoptotic stimuli, as well as exogenous stimuli, such as chemotherapy drugs and radiation. The defective apoptosis seen in human cancers often results from overexpression of antiapoptotic proteins in the Bcl-2 protein family, particularly Bcl-2 and Bcl-X(L). A great deal of effort is currently aimed at developing novel agents to inhibit the expression or function of these proteins. Antisense agents directed against Bcl-2 mRNA are showing considerable promise in clinical trials. In addition, detailed knowledge of the structures of Bcl-2 and Bcl-X(L), coupled with high-throughput and computer-assisted screening of chemical libraries, has led to the identification of a number of short peptides and small organic molecules capable of inhibiting Bcl-2 and Bcl-X(L) function. These newly described agents hold considerable promise for enhancing the chemo- and radiation sensitivities of Bcl-2- and Bcl-X(L)-overexpressing cancers. This review will highlight recent advances in the development and testing of agents targeting cell death inhibitors in the Bcl-2 protein family.

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ACCESSION NUMBER: 2003391785 EMBASE
TITLE: Role of caspases in renal tubular epithelial cell injury.
AUTHOR: Kaushal G.P.
CORPORATE SOURCE: Dr. G.P. Kaushal, Department of Medicine, Univ. of Arkansas for Med. Sciences, 4301 W. Markham St, Little Rock, AR 72205, United States. gkaushal@uams.edu
SOURCE: Seminars in Nephrology, (2003) 23/5 (425-431).
Refs: 78
ISSN: 0270-9295 CODEN: SNEPDJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The regulation of cell death has been investigated in a number of clinical disorders including renal ischemic and toxic acute renal failure. Caspases play a crucial role in the execution or final phase of cell death by cleaving and inactivating various structural and functional intracellular proteins that are essential for cell survival and proliferation. Evidence is now emerging to implicate the caspase pathway in a variety of renal diseases including the pathogenesis of acute renal failure. Among the 14 known members of the caspase family thus far identified several executioner caspases including caspases-3, -6, and -7 and the proinflammatory caspase including caspase-1 may participate in the final degradation of intracellular proteins. The activation of these caspases is regulated by the receptor- and mitochondrial-mediated cell signaling pathways as well as by the endoplasmic reticulum stress response. While the role of some caspases in renal injury is emerging, the roles of various proinflammatory and other executioner caspases remain to be determined. Although many pro- and anti-apoptotic molecules that act upstream of caspase activation have been identified, their regulation is yet to be determined in the pathogenesis of renal injury. A precise description of caspase-mediated cell death pathway and regulation of caspase activation is, therefore, critical to the understanding of the mechanism of renal injury and to the development of therapeutic targets that prevent renal diseases and preserve renal function. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L22 ANSWER 16 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003253582 EMBASE
TITLE: Bcl-2 proteins: Targets and tools for chemosensitisation of tumor cells.
AUTHOR: Bettaieb A.; Dubrez-Daloz L.; Launay S.; Plenchette S.; Rebe C.; Cathelin S.; Solary E.
CORPORATE SOURCE: E. Solary, INSERM U517, IFR 100, 7 Boulevard Jeanne d'Arc, 21000 Dijon, France. esolary@u-bourgogne.fr
SOURCE: Current Medicinal Chemistry - Anti-Cancer Agents, (2003) 3/4 (307-318).
Refs: 145
ISSN: 1568-0118 CODEN: CMCACI
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Proteins of the Bcl-2 family share one or several Bcl-2 homology (BH) regions and behave as pro- or anti-apoptotic proteins. Prosurvival members such as Bcl-2 and Bcl-X(L) are supposed to preserve mitochondrial outer membrane integrity, thus preventing the release of soluble apoptogenic molecules. Pro-apoptotic members include BH3-only proteins that act as sensors of cellular damage and initiate the death process and Bax-like proteins that act downstream of BH3-only proteins to permeabilise the mitochondrial outer membrane. Whether BH3-only proteins directly activate Bax-like proteins or prevent prosurvival members of the family from inhibiting Bax-like proteins or both remains a matter of controversy. Expression of these proteins is altered in various human tumours and this abnormal expression may contribute to oncogenesis and tumour cell resistance to anticancer drug-induced cell death. Based on these observations, prosurvival proteins are attractive intracellular targets for inducing tumour cell death or sensitising tumour cells to death induced by chemotherapeutic drugs. The use of 18-mer antisense oligonucleotides (G3139 or Genasense) targeting the first six codons of bcl-2 mRNA is currently developed in clinics with phase I studies demonstrating that thrombocytopenia may be the main dose-limiting side effect. This strategy, that efficiently decreases Bcl-2 protein expression in some tumour cells, is currently tested in phase II and phase III trials. Alternative approaches to achieve the functional knock-out of Bcl-2 include the use of either peptides mimicking the BH3 domain of Bcl-2-related proteins or more stable, non peptidic BH3 mimetics and the pharmacological modulation of the post-translational modifications of the protein.

L22 ANSWER 17 OF 47 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003247369 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12769779
TITLE: The BCL2-family of protein ligands as cancer drugs: the next generation of therapeutics.
AUTHOR: Liu WenJing; Bulgaru Anca; Haigentz Missak; Stein C A; Perez-Soler Roman; Mani Sridhar
CORPORATE SOURCE: Albert Einstein Comprehensive Cancer Center, Albert Einstein College of Medicine, Bronx, NY 10461, USA.
SOURCE: Current medicinal chemistry. Anti-cancer agents, (2003 May) 3 (3) 217-23. Ref: 22
Journal code: 101123597. ISSN: 1568-0118.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030529
Last Updated on STN: 20030713
Entered Medline: 20030711

AB Selective aberrant cell suicide (ie., apoptosis or programmed cell death) is a hallmark of "nonneoplastic" tissue. In cells that have clonally evolved or in common parlance "cancer cells", apoptosis is either itself aberrant or completely inhibited. Strategies to enhance apoptosis under conditions of cancer cellular stress is an evolving and actively investigated area of experimental therapeutics. Bcl2 proteins are key mediators of the process of apoptosis and ligands to these family of proteins have been described using modern combinatorial, computational and evolutionary small molecule screening approaches. Crystallization of several of the Bcl2 family members has provided clarification of the role of these ligands and provided a clearer mechanism of action for the consequences of ligand binding. In several cases, these ligands (e.g., HA14-1, 2-methoxy antimycin A) induce apoptosis even under conditions of Bcl2 overexpression and if developed preclinically will be promising anticancer agents. This rationale becomes even more striking when one observes overexpression of Bcl2 in 70% of breast cancer, 30-60% of prostate cancer, 80% of B-cell lymphomas, 90% of colorectal adenocarcinomas, and many other forms of cancer.

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 18 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003475462 EMBASE
TITLE: Targeting Bcl-2 and Bcl-X(L) with Nonpeptidic Small-Molecule Antagonists.
AUTHOR: Wang S.; Yang D.; Lippman M.E.
CORPORATE SOURCE: Dr. M.E. Lippman, Dept. Int. Med./Compreh. Cancer Ctr., Univ. of Michigan Medical School, 3101 Taubman Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109, United States
SOURCE: Seminars in Oncology, (2003) 30/5 SUPPL. 16 (133-142). Refs: 61
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Members of the Bcl-2 family of proteins are crucial regulators of programmed cell death or apoptosis. This family of proteins now includes both anti-apoptotic molecules such as Bcl-2 and Bcl-X(L), and pro-apoptotic molecules such as Bax, Bak, Bid, and Bad. The majority of human cancers are found to have overexpression of Bcl-2, Bcl-X(L), or both. Bcl-2 and Bcl-X(L) may play a critical role in cancer progression. Cancers with high levels of Bcl-2 or Bcl-X(L) or both proteins are resistant to a wide spectrum of chemotherapeutic agents and radiation therapy. Bcl-2 and Bcl-X(L) have become attractive targets for designing new anticancer drugs. Small-molecule inhibitors that are capable of inhibiting the activity of Bcl-2 and Bcl-X(L) may have great therapeutic potential as an entirely new class of anticancer drugs for treating many forms of cancers in which Bcl-2 and/or Bcl-X(L) proteins are overexpressed and for which traditional therapies are ineffective. Design of small-molecule inhibitors of Bcl-2 and Bcl-X(L) is a very new and exciting area for current anticancer drug design and development. In this article we will provide a brief review on the strategy and recent progress in designing small-molecule antagonists targeting Bcl-2 and Bcl-X(L). .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L22 ANSWER 19 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003287228 EMBASE
TITLE: Reversal of Bcl-2 mediated resistance of the EW36 human b-cell lymphoma cell line to arsenite- and pesticide-induced apoptosis by PK11195, a ligand of the mitochondrial benzodiazepine receptor.
AUTHOR: Muscarella D.E.; O'Brien K.A.; Lemley A.T.; Bloom S.E.
CORPORATE SOURCE: K.A. O'Brien, Dept. of Microbiology/Immunology, Cornell University, Ithaca, NY 14853, United States. dem10@cornell.edu
SOURCE: Toxicological Sciences, (1 Jul 2003) 74/1 (66-73). Refs: 33
ISSN: 1096-6080 CODEN: TOSCF2
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Opening of the permeability transition (PT) pore is a central feature of apoptosis induction by chemical stress. One component of the PT pore, the mitochondrial benzodiazepine receptor (mBzR), has recently received attention for its potential role in modulating PT pore function. Specifically, antagonistic ligands of the mBzR, such as 1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline-carboxamide (PK11195), have been shown to sensitize Bcl-2 overexpressing cells to apoptosis induction by facilitating the opening of the PT pore and the subsequent loss of mitochondrial membrane potential ($\Delta\psi(m)$). We examined whether PK11195 can sensitize EW36, a human B-cell lymphoma cell line that over-expresses Bcl-2, to apoptosis induction and mitochondrial depolarization by environmental chemicals including mitochondrial toxicants. We found that, although EW36 cells are refractory to apoptosis induction by antimycin A, rotenone, pyridaben, alachlor, and carbonyl cyanide m-chlorophenylhydrazone (mCICCP), they are dramatically sensitized to induction of apoptosis by low concentrations of these same agents following pretreatment with PK11195. The sensitization of EW36 cells is accompanied by a rapid and extensive loss of $\Delta\psi(m)$ within a few hours following chemical exposure. Furthermore, using sodium arsenite, we examined the role of the c-Jun N-terminal kinase (JNK) pathway and protein synthesis in apoptosis induction in EW36. We found that, unlike untreated cells, EW36 cells treated with PK11195 no longer show an association of JNK pathway activation with apoptosis induction. Importantly, PK11195 eliminates a requirement for protein synthesis in chemically induced apoptosis in EW36 cells. These results show significant drug-mediated alteration of cell sensitivity and JNK pathway activation to environmental chemicals and mitochondrial toxicants, following ligation of the mBzR.

L22 ANSWER 20 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003287221 EMBASE
TITLE: The mitochondrial benzodiazepine receptor as a potential target protein for drug development: Demonstration of functional significance with cell lines exhibiting differential expression of Bcl-2.
AUTHOR: Lash L.H.
CORPORATE SOURCE: L.H. Lash, Department of Pharmacology, Wayne State Univ. School of Med., 540 East Canfield Avenue, Detroit, MI 48201, United States. l.h.lash@wayne.edu
SOURCE: Toxicological Sciences, (1 Jul 2003) 74/1 (1-3). Refs: 16
ISSN: 1096-6080 CODEN: TOSCF2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The article highlighted in this issue is "Reversal of Bcl-2 Mediated Resistance of the EW36 Human B-Cell Lymphoma Cell Line to Arsenite and Pesticide-Induced Apoptosis by PK11195, a Ligand of the Mitochondrial Benzodiazepine Receptor" by Donna E. Muscarella, Kerry A. O'Brien, Ann T. Lemley, and Stephen E. Bloom from Cornell University in Ithaca, NY (pp. 66-73). The following brief review summarizes their findings, highlights the novel biological model and experimental approach used, and explores potential mechanistic and therapeutic implications of these findings.

L22 ANSWER 21 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2002241154 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11877388
TITLE: Hyperoxia-induced apoptosis does not require mitochondrial reactive oxygen species and is regulated by Bcl-2 proteins.
AUTHOR: Budinger G R Scott; Tso May; McClintock David S; Dean David A; Sznajder Jacob I; Chandel Navdeep S
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, Illinois 60611, USA.. s-buding@northwestern.edu
CONTRACT NUMBER: GM60472 (NIGMS)
HL67835-01 (NHLBI)
SOURCE: Journal of biological chemistry, (2002 May 3) 277 (18) 15654-60. Electronic Publication: 2002-02-27.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020430
Last Updated on STN: 20030105
Entered Medline: 20020702
AB Exposure of animals to hyperoxia results in lung injury that is characterized by apoptosis and necrosis of the alveolar epithelium and endothelium. The mechanism by which hyperoxia results in cell death, however, remains unclear. We sought to test the hypothesis that exposure to hyperoxia causes mitochondria-dependent apoptosis that requires the generation of reactive oxygen species from mitochondrial electron transport. Ratla cells exposed to hyperoxia underwent apoptosis characterized by the release of cytochrome c, activation of caspase-9, and nuclear fragmentation that was prevented by the overexpression of Bcl-X(L.) Murine embryonic fibroblasts from bax(-/-) bak(-/-) mice were resistant to hyperoxia-induced cell death. The administration of the antioxidants manganese (III) tetrakis (4-benzoic acid) porphyrin, ebselen, and N-acetylcysteine failed to prevent cell death following exposure to hyperoxia. Human fibrosarcoma cells (HT1080) lacking mitochondrial DNA (rho(0) cells) that failed to generate reactive oxygen species during exposure to hyperoxia were not protected against cell death following exposure to hyperoxia. We conclude that exposure to hyperoxia results in apoptosis that requires Bax or Bak and can be prevented by the overexpression of Bcl-X(L). The mitochondrial generation of reactive oxygen species is not required for cell death following exposure to hyperoxia.

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 22 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003048341 EMBASE
TITLE: Chemotherapy: Targeting the mitochondrial cell death pathway.
AUTHOR: Debatin K.-M.; Poncet D.; Kroemer G.
CORPORATE SOURCE: K.-M. Debatin, University Childrens Hospital, Prittwitzstrasse 43, D-89075 Ulm, Germany. klaus-michael.debatin@medizin.uni-ulm.de
SOURCE: Oncogene, (12 Dec 2002) 21/57 (8786-8803). Refs: 186
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB One of the mechanisms by which chemotherapeutics destroy cancer cells is by inducing **apoptosis**. **Apoptosis** can be activated through several different signalling pathways, but these all appear to converge at a single event - mitochondrial membrane permeabilization (MMP). This 'point-of-no-return' in the cell death program is a complex process that is regulated by the composition of the mitochondrial membrane and pre-mitochondrial signal-transduction events. MMP is subject to a complex regulation, and local alterations in the composition of mitochondrial membranes, as well as alterations in pre-mitochondrial signal-transducing events, can determine chemotherapy resistance in cancer cells. Detecting MMP might thus be useful for detecting chemotherapy responses in vivo. Several cytotoxic drugs induce MMP by a direct action on mitochondria. This type of agents can enforce death in cells in which upstream signals normally leading to **apoptosis** have been disabled. Cytotoxic components acting on mitochondria can specifically target proteins from the **Bcl-2** family, the peripheral benzodiazepin receptor, or the adenine nucleotide translocase, and/or act by virtue of their physicochemical properties as steroid analogues, cationic ampholytes, redox-active compounds or photosensitizers. Some compounds acting on mitochondria can overcome the cytoprotective effect of **Bcl-2**-like proteins. Several agents which are already used in anti-cancer chemotherapy can induce MMP, and new drugs specifically designed to target mitochondria are being developed.

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on STN

ACCESSION NUMBER: 2002134067 EMBASE
TITLE: Inhibition of protein-protein association by small molecules: Approaches and progress.
AUTHOR: Toogood P.L.
CORPORATE SOURCE: P.L. Toogood, Department of Medicinal Chemistry, Pfizer Global Res. and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, United States. Peter.toogood2@pfizer.com
SOURCE: Journal of Medicinal Chemistry, (11 Apr 2002) 45/8 (1543-1558). Refs: 92
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

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on STN

ACCESSION NUMBER: 2002408618 EMBASE
TITLE: Mitochondrial **apoptosis** and the peripheral benzodiazepine receptor: A novel target for viral and pharmacological manipulation.
AUTHOR: Castedo M.; Perfettini J.-L.; Kroemer G.
CORPORATE SOURCE: Dr. G. Kroemer, CNRS-UMR 1599, Institut Gustave Roussy, Pavillon de Recherche 1, 39 rue Camille-Desmoulins, F-94805 Villejuif, France. kroemer@igr.fr
SOURCE: Journal of Experimental Medicine, (4 Nov 2002) 196/9 (1121-1125). Refs: 27
ISSN: 0022-1007 CODEN: JEMEAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

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on STN

ACCESSION NUMBER: 2002267123 EMBASE
TITLE: A view to a kill: Ligands for **Bcl-2** family proteins.
AUTHOR: Rutledge S.E.; Chin J.W.; Schepartz A.
CORPORATE SOURCE: S.E. Rutledge, Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520-8107, United States
SOURCE: Current Opinion in Chemical Biology, (1 Aug 2002) 6/4 (479-485). Refs: 49
ISSN: 1367-5931 CODEN: COCBF4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Apoptosis** is the essential process of programmed cell death that, in multicellular organisms, regulates development and maintains homeostasis. Defects in the apoptotic molecular machinery that result in either excessive or insufficient **apoptosis** are observed in a remarkably wide range of human disease, prompting intense interest in pro- and anti-apoptotic proteins as therapeutic targets. A number of recent reports have described the discovery of ligands for anti-apoptotic **Bcl-2** family proteins by a variety of approaches, including computational, combinatorial and evolutionary strategies. Both the design of ligands and the exploration of their mechanisms of action have been greatly enhanced by recent high-resolution structure determinations of proteins from this family. Several of the newly discovered ligands promote **apoptosis**, and some do so even in the face of overexpressed anti-apoptotic **Bcl-2** proteins. Ligands that overcome the protective effects associated with up-regulation of anti-apoptotic **Bcl-2** proteins represent especially promising therapeutic leads.

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 26 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2002215327 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11952418
TITLE: Respiration and mitochondrial membrane potential are not required for **apoptosis** and anti-apoptotic action of **Bcl-2** in HeLa cells.
AUTHOR: Shchepina L A; Popova E N; Pletjushkina O Yu; Chernyak B V
CORPORATE SOURCE: Department of Cell Physiology and Immunology, School of Biology, Lomonosov Moscow State University, Moscow, 119899 Russia.
SOURCE: Biochemistry. Biokhimiia, (2002 Feb) 67 (2) 222-6. Journal code: 0376536. ISSN: 0006-2979.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020416
Last Updated on STN: 20020814
Entered Medline: 20020813

AB The release of cytochrome c from intermembrane space of mitochondria into cytosol is one of the critical events in apoptotic cell death. The important anti-apoptotic oncoprotein **Bcl-2** inhibits this process. In the present study it was shown that **apoptosis** and release of cytochrome c induced by staurosporine or by tumor necrosis factor-alpha in HeLa cells were not affected by inhibitors of respiration (rotenone, myxothiazol, antimycin A) or by uncouplers (CCCP, DNP) that decrease the membrane potential at the inner mitochondrial membrane. The inhibitors of respiration and the uncouplers did not affect also the anti-apoptotic activity of **Bcl-2**.

L22 ANSWER 27 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2002353481 EMBASE
TITLE: **Mitochondria** and **apoptosis**: New therapeutic targets.
AUTHOR: Hockenbery D.M.; Giedt C.D.; O'Neill J.W.; Manion M.K.; Banker D.E.
CORPORATE SOURCE: D.M. Hockenbery, Division of Human Biology, Fred Hutchinson
Cancer Res. Center, Seattle, WA 98109, United States
SOURCE: Advances in Cancer Research, (2002) 85/- (203-242). Refs: 203
ISSN: 0065-230X CODEN: ACRSAJ
COUNTRY: United States
DOCUMENT TYPE: Journal: General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L22 ANSWER 28 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2002305109 EMBASE
TITLE: The permeability transition pore complex: Another view.
AUTHOR: Halestrap A.P.; McStay G.P.; Clarke S.J.
CORPORATE SOURCE: A.P. Halestrap, Department of Biochemistry, University of Bristol, Bristol BS8 1TD, United Kingdom.
A.Halestrap@Bristol.ac.uk
SOURCE: Biochimie, (2002) 84/2-3 (153-166). Refs: 86
ISSN: 0300-9084 CODEN: BICMBE
PUBLISHER IDENT.: S 0300-9084(02)01375-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
018 Cardiovascular Diseases and Cardiovascular Surgery
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Mitochondria play a critical role in initiating both apoptotic and necrotic cell death. A major player in this process is the mitochondrial permeability transition pore (MPTP), a non-specific pore, permeant to any molecule of < 1.5 kDa, that opens in the inner mitochondrial membrane under conditions of elevated matrix [Ca(2+)], especially when this is accompanied by oxidative stress and depleted adenine nucleotides. Opening of the MPTP causes massive swelling of mitochondria, rupture of the outer membrane and release of intermembrane components that induce **apoptosis**. In addition mitochondria become depolarised causing inhibition of oxidative phosphorylation and stimulation of ATP hydrolysis.
Pore opening is inhibited by cyclosporin A analogues with the same affinity as they inhibit the peptidyl-prolyl cis-trans isomerase activity of mitochondrial cyclophilin (CyP-D). These data and the observation that different ligands of the adenine nucleotide translocase (ANT) can either stimulate or inhibit pore opening led to the proposal that the MPTP is formed by a Ca-triggered conformational change of the ANT that is facilitated by the binding of CyP-D. Our model is able to explain the mode of action of a wide range of known modulators of the MPTP that exert their effects by changing the binding affinity of the ANT for CyP-D, Ca(2+) or adenine nucleotides. The extensive evidence for this model from our own and other laboratories is presented, including reconstitution studies that demonstrate the minimum configuration of the MPTP to require neither the voltage activated anion channel (VDAC or porin) nor any other outer membrane protein. However, other proteins including **Bcl-2**, BAX and virus-derived proteins may interact with the ANT to regulate the MPTP. Recent data suggest that oxidative cross-linking of two matrix facing cysteine residues on the ANT (Cys(56) and Cys(159)) plays a key role in regulating the MPTP. Adenine nucleotide binding to the ANT is inhibited by Cys(159) modification whilst oxidation of Cys(56) increases CyP-D binding to the ANT, probably at Pro(61). .COPYRGT. 2002 Societe francaise de biochimie et biologie moleculaire / Editions scientifiques et medicales Elsevier SAS. All rights reserved.

L22 ANSWER 28 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. (Continued)

L22 ANSWER 29 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003262634 EMBASE
TITLE: **Apoptosis** and the treatment of breast cancer.
AUTHOR: Cuello M.A.; Nau M.; Lipkowitz S.
CORPORATE SOURCE: Dr. M.A. Cuello, Ginecologic Oncology Section, Department of Obstetrics/Gynecology, Pontificia Universidad Catolica, Santiago, Chile. macuello@med.puc.cl
SOURCE: Breast Disease, (2002) 15/- (71-82).
Refs: 154
ISSN: 0888-6008 CODEN: BRDIES
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Dysregulation of **apoptosis** plays a major role in cancer etiology. Cancer cells often contain genetic abnormalities which allow the cells to survive under conditions that normally would trigger their demise. The identification of these mutations has changed the models of cancer progression from a disease of excessive proliferation to one of unbalanced cell death and cell growth. During the last decade, fundamental knowledge delineating the molecular mechanisms of **apoptosis** has emerged and now can be exploited to identify novel apoptotic modulators for the treatment of cancer.

L22 ANSWER 30 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2002293944 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12034471
TITLE: **Bcl-2** protects against **apoptosis** induced by antimycin A and bongkrekic acid without restoring cellular ATP levels.
AUTHOR: de Graaf Aniek O; Meijerink Jules P P; van den Heuvel Lambert P; DeAbreu Ronney A; de Witte Theo; Jansen Joop H; Smeitink Jan A M
CORPORATE SOURCE: Central Hematology Laboratory/Department of Hematology, University Medical Center Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.. a.degraaf@chl.azn.nl
SOURCE: Biochimica et biophysica acta, (2002 Apr 22) 1554 (1-2) 57-65.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020530
Last Updated on STN: 20020803
Entered Medline: 20020802
AB Several studies indicate that mitochondrial ATP production as well as ADP/ATP exchange across mitochondrial membranes are impaired during **apoptosis**. We investigated whether **Bcl-2** could protect against cell death under conditions in which ATP metabolism is inhibited. Inhibition of ATP production using antimycin A (AA) (complex III inhibition) combined with inhibition of ADP/ATP exchange by bongkrekic acid (BA) (adenine nucleotide translocator (ANT) inhibition) induced a sharp decrease in total cellular ATP in FL5.12 parental cells (to 35% of untreated controls after 24 h of incubation). Within 24 and 48 h, 38% and 75% of the cells had died, respectively. However, in stably transfected FL5.12 **Bcl-2** subclones, no cell death occurred under these experimental conditions. Similar results were obtained with Jurkat and **Bcl-2** overexpressing Jurkat cells. Total cellular ATP levels were equally affected in FL5.12 **Bcl-2** overexpressing cells and FL5.12 parental cells. This indicates that **Bcl-2** overexpressing cells are able to survive with very low cellular ATP content. Furthermore, **Bcl-2** did not protect against cell death by restoring ATP levels. This suggests that, under these conditions, **Bcl-2** acts by inhibiting the signalling cascade triggered by the inhibitors that would normally lead to **apoptosis**.

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on STN
ACCESSION NUMBER: 2002200431 EMBASE
TITLE: **Bcl-2** protects against **apoptosis** induced by antimycin A and bongkrekic acid without restoring cellular ATP levels.
AUTHOR: De Graaf A.O.; Meijerink J.P.P.; Van den Heuvel L.P.; DeAbreu R.A.; De Witte T.; Jansen J.H.; Smeitink J.A.M.
CORPORATE SOURCE: A.O. De Graaf, Central Hematology Laboratory, Department of Hematology, University Medical Center Nijmegen, P.O. Box 9101, 6500 HB, Nijmegen, Netherlands. a.degraaf@chl.azn.nl
SOURCE: Biochimica et Biophysica Acta - Bioenergetics, (22 Apr 2002) 1554/1-2 (57-65).
Refs: 52
ISSN: 0005-2728 CODEN: BBBEB4
PUBLISHER IDENT.: S 0005-2728(02)00213-X
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Several studies indicate that mitochondrial ATP production as well as ADP/ATP exchange across mitochondrial membranes are impaired during **apoptosis**. We investigated whether **Bcl-2** could protect against cell death under conditions in which ATP metabolism is inhibited. Inhibition of ATP production using antimycin A (AA) (complex III inhibition) combined with inhibition of ADP/ATP exchange by bongkrekic acid (BA) (adenine nucleotide translocator (ANT) inhibition) induced a sharp decrease in total cellular ATP in FL5.12 parental cells (to 35% of untreated controls after 24 h of incubation). Within 24 and 48 h, 38% and 75% of the cells had died, respectively. However, in stably transfected FL5.12 **Bcl-2** subclones, no cell death occurred under these experimental conditions. Similar results were obtained with Jurkat and **Bcl-2** overexpressing Jurkat cells. Total cellular ATP levels were equally affected in FL5.12 **Bcl-2** overexpressing cells and FL5.12 parental cells. This indicates that **Bcl-2** overexpressing cells are able to survive with very low cellular ATP content. Furthermore, **Bcl-2** did not protect against cell death by restoring ATP levels. This suggests that, under these conditions, **Bcl-2** acts by inhibiting the signalling cascade triggered by the inhibitors that would normally lead to **apoptosis**.

L22 ANSWER 32 OF 47 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001382935 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11305906
TITLE: Biophysical characterization of recombinant human **Bcl-2** and its interactions with an inhibitory ligand, antimycin A.
AUTHOR: Kim K M; Giedt C D; Basanez G; O'Neill J W; Hill J J; Han Y H; Tzung S P; Zimmerberg J; Hockenbery D M; Zhang K Y
CORPORATE SOURCE: Divisions of Basic Sciences and Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington 98109, USA.
CONTRACT NUMBER: CA15704-26 (NCI)
SOURCE: Biochemistry, (2001 Apr 24) 40 (16) 4911-22.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705
AB **Apoptosis** is an essential physiological process, regulated by the family of **Bcl-2**-related proteins. However, the molecular mechanism by which **Bcl-2** regulates **apoptosis** still remains elusive. Here we report the functional studies of recombinant human **Bcl-2** with the deletion of 22 residues at the C-terminal membrane-anchoring region (rhBcl-2Delta22). Characterization of rhBcl-2Delta22 showed that the recombinant protein is homogeneous and monodisperse in nondenaturing solutions, stable at room temperature in the presence of a metal chelator, and an alpha-helical protein with unfolding of secondary structure at a T(m) of 62.8 degrees C. Optimal membrane pore formation by rhBcl-2Delta22 required negatively charged phospholipids. The existence of a hydrophobic groove in rhBcl-2Delta22 was demonstrated by the fluorescence enhancement of the hydrophobic ANS probe with which a pro-apoptotic Bak BH3 peptide competed. The respiratory inhibitor antimycin A also bound to the hydrophobic groove of rhBcl-2Delta22 with a K(d) of 0.82 microM. The optimal binding conformation of antimycin A was predicted from molecular docking of antimycin A with the hBcl-2 model created by homology modeling. Antimycin A selectively induces **apoptosis** in cells overexpressing **Bcl-2**, suggesting that hydrophobic groove-binding compounds may act as selective apoptotic triggers in tumor cells.

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ACCESSION NUMBER: 2001360727 EMBASE
TITLE: Increased lactate production follows loss of mitochondrial membrane potential during apoptosis of human leukaemia cells.
AUTHOR: Tiefenthaler M.; Amberger A.; Bacher N.; Hartmann B.L.; Margreiter R.; Kofler R.; Konwalinka G.
CORPORATE SOURCE: M. Tiefenthaler, Department of Internal Medicine, Innsbruck
University Hospital, Anichstrasse 35, A-6020 Innsbruck, Austria. martin.tiefenthaler@uibk.ac.at
SOURCE: British Journal of Haematology, (2001) 114/3 (574-580). Refs: 29
ISSN: 0007-1048 CODEN: BJHEAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Acute tumour-lysis syndrome (ATLS) is a frequently fatal complication after cytoreductive leukaemia therapy. Lactic acidosis is associated with ATLS and its extent is correlated with the severity of ATLS. In the course of cytoreductive therapy, **apoptosis** is induced in tumour cells, which results in loss of mitochondrial function. We hypothesize that loss of mitochondrial function leads to compensatory glycolysis, which is the main cause of lactate accumulation and acidosis. We tested this hypothesis using the model of glucocorticoid-induced **apoptosis** in the human acute lymphoblastic leukaemia cell line CCRF-CEM. After induction of glucocorticoid-induced **apoptosis**, a biphasic course of lactate production was observed. Prior to the onset of **apoptosis**, i.e. prior to the loss of membrane potential, lactate production was reduced. However, subsequent to loss of mitochondrial membrane potential a massive increase in lactate production was observed (15.5±0.5 versus 10.17±0.09 mmol/10(6) cells, P=0.001). We also demonstrated that inhibition of respiratory chain activity by antimycin A resulted in excess lactate production. In the model cell line used, conditional **bcl -2** expression delayed glucocorticoid-induced **apoptosis** by protecting against loss of mitochondrial membrane potential; **bcl-2** expression delayed the increase in lactate production and had no effect on the pre-apoptotic drop in lactate production. **Apoptosis**-induced lactate production was also observed in other cell lines (HL60, THP1 and OPM2) with various cytotoxic agents [doxorubicin, gemcitabine and vumon (VM26)]. Thus, the data suggest that lactate acidosis can be caused by apoptotic loss of mitochondrial function and massive **apoptosis** of a tumour mass via lactic acidosis may be the essential pathological event in ATLS.

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ACCESSION NUMBER: 2001410816 EMBASE
TITLE: Synthetic peptides and non-peptidic molecules as probes of structure and function of **Bcl-2** family proteins and modulators of **apoptosis**.
AUTHOR: Liu D.; Huang Z.
CORPORATE SOURCE: Z. Huang, Department of Biochemistry, University of Illinois, 302 Burrill Hall, 407 South Goodwin Avenue, Urbana, IL 61801, United States. z-huang@life.uiuc.edu
SOURCE: Apoptosis, (2001) 6/6 (453-462). Refs: 73
ISSN: 1360-8185 CODEN: APOPFN
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The **Bcl-2** family includes a growing number of proteins that play an essential role in regulating **apoptosis** or programmed cell death. Members of this family display diverse biological functions and can either inhibit or promote cell death signals. Abnormal gene expression of some **Bcl-2** family members such as **Bcl-2** that inhibits **apoptosis** is found in a wide variety of human cancers and contributes to the resistance of tumor cells to conventional therapies through interfering with the cell death signals triggered by chemotherapeutic agents. As such, elucidating the structure-function and mechanism of the **Bcl-2** family is important for understanding some of the fundamental principles underling the death and survival of cells and of practical value for developing potential therapeutics to control **apoptosis** in pathological processes. Synthetic peptides derived from homologous or heterogeneous domains in **Bcl-2** family proteins that might mediate different biological activities provide simplified and experimentally more tractable models as compared to their full-length counterparts to dissect and analyze the complex functional roles of these proteins. Non-peptidic molecules identified from random screening of natural products or designed by rational structure-based techniques can mimic the effect of synthetic peptides by targeting similar active sites on a **Bcl-2** family member protein. In this article, we review recent progress in using these synthetic peptides and non-peptidic mimic molecules to obtain information about the structure and function of **Bcl-2** family proteins and discuss their application in modulating and studying intracellular apoptotic signaling.

L22 ANSWER 35 OF 47 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2001440272 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11485385
TITLE: Differential induction of **apoptosis** and MAP kinase signaling by mitochondrial toxicants in drug-sensitive compared to drug-resistant B-lineage lymphoid cell lines.
AUTHOR: O'Brien K A; Muscarella D E; Bloom S E
CORPORATE SOURCE: Department of Microbiology and Immunology, Cornell University, Ithaca, New York 14853, USA.
CONTRACT NUMBER: ES07052 (NIEHS)
SOURCE: Toxicology and applied pharmacology, (2001 Aug 1) 174 (3) 245-56.
Journal code: 0416575. ISSN: 0041-008X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

AB A panel of human B-lineage lymphoma cell lines differing in cancer drug-resistance status and **Bcl-2**/Bax expression were used to study the contribution of mitochondrial-based perturbations and regulation in differential induction of **apoptosis**. Mitochondrial dysfunction was induced in cells by the uncoupler carbonyl cyanide m-chlorophenylhydrazone (mClCCP) and the respiratory chain inhibitor antimycin A. Cells were then assayed for early changes in MAP kinase signaling and subsequent induction of **apoptosis**. The cancer drug-resistant cell lines EW36 and CA46, overexpressing **Bcl -2** and deficient in Bax, respectively, were both resistant to mitochondrial toxicant-induced cleavage of poly(ADP-ribose) polymerase (PARP) and morphologically detectable apoptotic cell death. In contrast, cancer drug-sensitive ST486 cell line, with low **Bcl-2** expression, was sensitive to PARP cleavage and **apoptosis** engagement. Interestingly, mClCCP induced twofold more **apoptosis** than antimycin A in the ST486 cells. Exposure to the mitochondrial toxicants resulted in the early and preferential activation of the ERK and p38 MAP kinase pathways in only the drug-sensitive ST486 cell line, with mClCCP more potent than antimycin A. Specific inhibition of the p38 pathway augmented baseline and mClCCP-induced **apoptosis**. These results show that multi-drug-resistant and -sensitive B-lineage cells are also resistant and sensitive to compounds inducing mitochondrial dysfunction. The differential sensitivity to mitochondrial toxicant effects involved regulation by MAP kinases, since ERK and p38 were found to be preferentially activated only in the drug-sensitive B-lineage cells. Modulation of the p38 signaling pathway altered the sensitivity of cells to mitochondrial stress and may play a more general role in regulating the sensitivity of B-lineage cells to drugs and environmental toxicants. Copyright 2001 Academic Press.

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on STN

ACCESSION NUMBER: 2001137232 EMBASE
TITLE: Small, but deadly: Small-molecule inhibition of **Bcl -2** homologue heterodimerization.
AUTHOR: Dewson G.
CORPORATE SOURCE: . gd11@le.ac.uk
SOURCE: Trends in Biochemical Sciences, (1 Apr 2001) 26/4 (218-219). Refs: 2
ISSN: 0968-0004 CODEN: TBSCDB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

Searched by: Mary Hale 571-272-2507 REM 1D86

L22 ANSWER 37 OF 47 MEDLINE on STN
ACCESSION NUMBER: 2001180202 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11175751
TITLE: Antimycin A mimics a cell-death-inducing Bcl-2 homology domain 3.
COMMENT: Comment in: Nat Cell Biol. 2001 Feb;3(2):E43-6. PubMed ID: 11175758
AUTHOR: Tzung S P; Kim K M; Basanez G; Giedt C D; Simon J; Zimmerberg J; Zhang K Y; Hockenbery D M
CORPORATE SOURCE: Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, Washington, 98195 USA.
CONTRACT NUMBER: CA15704-26 (NCI)
SOURCE: Nature cell biology, (2001 Feb) 3 (2) 183-91. Journal code: 100890575. ISSN: 1465-7392.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
AB The Bcl-2-related survival proteins confer cellular resistance to a wide range of agents. Bcl-xL-expressing hepatocyte cell lines are resistant to tumour necrosis factor and anti-cancer drugs, but are more sensitive than isogenic control cells to antimycin A, an inhibitor of mitochondrial electron transfer. Computational molecular docking analysis predicted that antimycin A interacts with the Bcl-2 homology domain 3 (BH3)-binding hydrophobic groove of Bcl-xL. We demonstrate that antimycin A and a Bak BH3 peptide bind competitively to recombinant Bcl-2. Antimycin A and BH3 peptide both induce mitochondrial swelling and loss of DeltaPsim on addition to mitochondria expressing Bcl-xL. The 2-methoxy derivative of antimycin A3 is inactive as an inhibitor of cellular respiration but still retains toxicity for Bcl-xL+ cells and mitochondria. Finally, antimycin A inhibits the pore-forming activity of Bcl-x L in synthetic liposomes, demonstrating that a small non-peptide ligand can directly inhibit the function of Bcl-2-related proteins.

L22 ANSWER 38 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2001091332 EMBASE
TITLE: Bcl-2 family proteins as targets for anticancer drug design.
AUTHOR: Huang Z.
CORPORATE SOURCE: Z. Huang, Department of Biochemistry, University of Illinois, Urbana, IL 61801, United States
SOURCE: Oncogene, (27 Dec 2000) 19/56 (6627-6631). Refs: 33
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Bcl-2 family proteins are key regulators of programmed cell death or apoptosis that is implicated in many human diseases, particularly cancer. In recent years, they have attracted intensive interest in both basic research to understand the fundamental principles of cell survival and cell death and drug discovery to develop a new class of anticancer agents. The Bcl-2 family includes both anti- and pro-apoptotic proteins with opposing biological functions in either inhibiting or promoting cell death. High expression of anti-apoptotic members such as Bcl-2 and Bcl-x(L) commonly found in human cancers contributes to neoplastic cell expansion and interferes with the therapeutic action of many chemotherapeutic drugs. The functional blockade of Bcl-2 or Bcl-x(L) could either restore the apoptotic process in tumor cells or sensitize these tumors for chemo- and radiotherapies. This article reviews the recent progress in the design and discovery of small molecules that block the anti-apoptotic function of Bcl-2 or Bcl-x(L). These chemical inhibitors are effective modulators of apoptosis and promising leads for the further development of new anticancer agents.

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on STN
ACCESSION NUMBER: 2000362288 EMBASE
TITLE: Small molecule inhibitors of Bcl-2 function: Modulators of apoptosis and promising anticancer agents.
AUTHOR: Huang Z.
CORPORATE SOURCE: Z. Huang, Department of Biochemistry, University of Illinois, Urbana, IL 61801, United States.
z-huang@uivc.edu
SOURCE: Current Opinion in Drug Discovery and Development, (2000) 3/5 (565-574). Refs: 37
ISSN: 1367-6733 CODEN: CODDFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Bcl-2 and related proteins play a central role in the regulation of programmed cell death or apoptosis implicated in many human diseases. As such, they have been prime targets for both basic research to understand the fundamental principles underlying the life and death of a cell, and for drug discovery, to develop a new generation of therapeutics for the treatment of cancer. Structure-function studies of the Bcl-2 family of proteins have revealed a surface pocket on anti-apoptotic Bcl-2 and Bcl-x(L) that is critical for their interaction with other pro-apoptotic proteins and their ability to suppress cell death signals. Intensive efforts have been made by a number of laboratories in both academia and the pharmaceutical industry to find small molecules that recognize this surface pocket of Bcl-2 or Bcl-x(L) and antagonize their biological functions. This article reviews the recent progress in the study of peptides, and non-peptidic natural and synthetic compounds that block the antiapoptotic function of Bcl-2 or Bcl-x(L). The design and discovery of these agents has opened new avenues in the basic research of Bcl-2-regulated apoptotic processes and the development of new anticancer drugs.

L22 ANSWER 40 OF 47 MEDLINE on STN
ACCESSION NUMBER: 1999393487 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10463952
TITLE: Overexpression of manganese superoxide dismutase protects against mitochondrial-initiated poly(ADP-ribose) polymerase-mediated cell death.
AUTHOR: Kiningham K K; Oberley T D; Lin S; Mattingly C A; St Clair D K
CORPORATE SOURCE: Graduate Center for Toxicology, University of Kentucky, Lexington, Kentucky 40536, USA.
CONTRACT NUMBER: CA49797 (NCI)
CA59835 (NCI)
HL03544 (NHLBI)
SOURCE: FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (1999 Sep) 13 (12) 1601-10. Journal code: 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990917
AB Mitochondria have recently been shown to serve a central role in programmed cell death. In addition, reactive oxygen species (ROS) have been implicated in cell death pathways upon treatment with a variety of agents; however, the specific cellular source of the ROS generation is unknown. We hypothesize that mitochondria-derived free radicals play a critical role in apoptotic cell death. To directly test this hypothesis, we treated murine fibrosarcoma cell lines, which expressed a range of mitochondrial manganese superoxide dismutase (MnSOD) activities, with respiratory chain inhibitors. Apoptosis was confirmed by DNA fragmentation analysis and electron microscopy. MnSOD overexpression specifically protected against cell death upon treatment with rotenone or antimycin. We examined bcl-x(L), p53 and poly(ADP-ribose) polymerase (PARP) to identify specific cellular pathways that might contribute to the mitochondrial-initiated ROS-mediated cell death. Cells overexpressing MnSOD contained less bcl-x(L) within the mitochondria compared to control (NEO) cells, therefore excluding the role of bcl-x(L). p53 was undetectable by Western analysis and examination of the proapoptotic protein bax, a p53 target gene, did not increase with treatment. Activation of caspase-3 (CPP-32) occurred in the NEO cells independent of cytochrome c release from the mitochondria. PARP, a target protein of CPP-32 activity, was cleaved to a 64 kDa fragment in the NEO cells prior to generation of nucleosomal fragments. Taken together, these findings suggest that mitochondrial-mediated ROS generation is a key event by which inhibition of respiration causes cell death, and identifies CPP-32 and the PARP-linked pathway as targets of mitochondrial-derived ROS-induced cell death.

Searched by: Mary Hale 571-272-2507 REM 1D86

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on STN

ACCESSION NUMBER: 1999062670 EMBASE
TITLE: Hydrogen peroxide-induced **apoptosis** is CD95-independent, requires the release of mitochondria-derived reactive oxygen species and the activation of NF-κB.
AUTHOR: Dumont A.; Hehner S.P.; Hofmann T.G.; Ueffing M.; Droge W.; Schmitz M.L.
CORPORATE SOURCE: M.L. Schmitz, Department of Immunochemistry, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
SOURCE: Oncogene, (21 Jan 1999) 18/3 (747-757).
Refs: 63
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Reactive oxygen species (ROS) play an important role in cell death induced by many different stimuli. This study shows that hydrogen peroxide-induced **apoptosis** in T-cells did not require tyrosine kinase p56(lck), phosphatase CD45, the CD95 receptor and its associated Caspase-8. H2O2-triggered cell death led to the induced cleavage and activation of Caspase-3. Hydrogen peroxide-treatment of T-cells resulted in the formation of mitochondrial permeability transition pores, a rapid decrease of the mitochondrial transmembrane potential ΔΨ(m) and the release of Cytochrome C. Inhibition of the mitochondrial permeability transition by bongkrekic acid (BA), or interference with the mitochondrial electron transport system by rotenone or menadione prevented the cytotoxic effect of H2O2. Antimycin A, a mitochondrial inhibitor that increases the release of mitochondrial ROS (MiROS), enhanced **apoptosis**. Overexpression of **Bcl-2** and the viral anti-apoptotic proteins BHRF-1 and E1B 19K counteracted N2O2-induced **apoptosis**. Pharmacological and genetic inhibition of transcription factor NF-κB protected cells from hydrogen peroxide-elicited cell death. This detrimental effect of NF-κB mediating hydrogen peroxide-induced cell death presumably relies on the induced expression of death effector genes such as p53, which was NF-κB-dependently upregulated in the presence of H2O2.

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ACCESSION NUMBER: 1998210164 EMBASE
TITLE: Nitric oxide regulates energy metabolism and **Bcl-2** expression in intestinal epithelial cells.
AUTHOR: Nishikawa M.; Takeda K.; Sato E.F.; Kuroki T.; Inoue M.
CORPORATE SOURCE: M. Nishikawa, Dept. of Biochemistry, Osaka City Univ. Medical School, 1-4-54 Asahimachi, Abeno-ku, Osaka 545, Japan
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1998) 274/5 37-5 (G797-G801).
Refs: 50
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Nitric oxide (NO) inhibits the respiration of mitochondria and enteric bacteria, particularly under low O2 concentration, and induces **apoptosis** of various types of cells. To gain insight into the molecular role of NO in the intestine, we examined its effects on the respiration, Ca2+ status, and expression of **Bcl-2** in cultured intestinal epithelial cells (IEC-6). NO reversibly inhibited the respiration of IEC-6 cells, especially under physiologically low O2 concentration. Although NO elevated cytosolic Ca2+ as determined by the fura 2 method, the cells were fairly resistant to NO. Kinetic analysis revealed that prolonged exposure to NO elevated the levels of **Bcl-2** and suppressed the NO-induced changes in Ca2+ status of the cells. Because **Bcl-2** possesses antiapoptotic function, toxic NO effects might appear minimally in enterocytes enriched with **Bcl-2**. Thus NO might effectively exhibit its antibacterial action in anaerobic intestinal lumen without inducing **apoptosis** of **Bcl-2**-enriched mucosal cells.

L22 ANSWER 43 OF 47 MEDLINE on STN

ACCESSION NUMBER: 1998054005 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9393856
TITLE: **Bcl-xL** regulates the membrane potential and volume homeostasis of mitochondria.
COMMENT: Comment in: Cell. 1997 Nov 28;91(5):559-62. PubMed ID: 9393848
AUTHOR: Vander Heiden M G; Chandel N S; Williamson E K; Schumacker P T; Thompson C B
CORPORATE SOURCE: Gwen Knapp Center and Committee on Immunology, Department of Medicine, University of Chicago, Illinois 60637, USA.
SOURCE: Cell, (1997 Nov 28) 91 (5) 627-37.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980116
Last Updated on STN: 19980116
Entered Medline: 19971229

AB Mitochondrial physiology is disrupted in either **apoptosis** or necrosis. Here, we report that a wide variety of apoptotic and necrotic stimuli induce progressive mitochondrial swelling and outer mitochondrial membrane rupture. Discontinuity of the outer mitochondrial membrane results in cytochrome c redistribution from the intermembrane space to the cytosol followed by subsequent inner mitochondrial membrane depolarization. The mitochondrial membrane protein **Bcl-xL** can inhibit these changes in cells treated with apoptotic stimuli. In addition, **Bcl-xL**-expressing cells adapt to growth factor withdrawal or staurosporine treatment by maintaining a decreased mitochondrial membrane potential. **Bcl-xL** expression also prevents mitochondrial swelling in response to agents that inhibit oxidative phosphorylation. These data suggest that **Bcl-xL** promotes cell survival by regulating the electrical and osmotic homeostasis of mitochondria.

L22 ANSWER 44 OF 47 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 96218652 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8668329
TITLE: Retardation of chemical hypoxia-induced necrotic cell death by **Bcl-2** and ICE inhibitors: possible involvement of common mediators in apoptotic and necrotic signal transductions.
AUTHOR: Shimizu S; Eguchi Y; Kamiike W; Waguri S; Uchiyama Y; Matsuda H; Tsujimoto Y
CORPORATE SOURCE: The First Department of Surgery, Osaka University Medical School, Japan.
SOURCE: Oncogene, (1996 May 16) 12 (10) 2045-50.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 20000303
Entered Medline: 19960808

AB Inhibition of the respiratory chain reaction by cyanide, rotenone or antimycin A (chemical hypoxia) induces necrotic cell death characterized by apparently intact chromatin, remarkable mitochondrial swelling with loss of crista structure, and loss of plasma membrane integrity. The treatments induce no apoptotic cell death, as defined by fragmented nuclei with condensed chromatin, fragmented or condensed cytoplasm. The anti-apoptotic proteins **Bcl-2** and **Bcl-xL** effectively retard the chemical hypoxia-induced necrotic cell death. The necrotic cell death is also retarded by inhibitors of ICE(-like) proteases, including interleukin-1beta converting enzyme (ICE), which are common mediators of **apoptosis**. These results indicate that **Bcl-2/Bcl-xL** and ICE(-like) proteases modulate apoptotic and at least some forms of necrotic cell death. Both cell death pathways appear to involve some common mediators; however necrotic or apoptotic cell death signals might be transduced through multiple pathways, because **Bcl-2/ Bcl-xL** or inhibitors of ICE(-like) proteases are relatively less potent in blocking necrotic cell death than in preventing **apoptosis**.

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L22 ANSWER 45 OF 47 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 96226523 EMBASE
DOCUMENT NUMBER: 1996226523
TITLE: **Bcl-2** blocks loss of mitochondrial membrane potential while ICE inhibitors act at a different step during inhibition of death induced by respiratory chain inhibitors.
AUTHOR: Shimizu S.; Eguchi Y.; Kamiike W.; Waguri S.; Uchiyama Y.; Matsuda H.; Tsujimoto Y.
CORPORATE SOURCE: Department of Medical Genetics, Biomedical Research Center,
Osaka University Medical School, 2-2 Yamadaoka,Suita 565, Japan
SOURCE: Oncogene, (1996) 13/1 (21-29).
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Bcl-2**, **Bcl-x**,, CrmA and tetrapeptide ICE inhibitor reduce the extent of necrotic cell death induced by cyanide, which primarily damages mitochondria. Although none of them affects the drastic decrease in ATP levels induced by cyanide, **Bcl-2** and **Bcl-x**(L) but not CrmA or ICE inhibitor inhibit the cyanide-induced decrease in mitochondrial membrane potential. A similar blocking effect is observed on necrotic cell death induced by other respiration inhibitors, rotenone and antimycin A, and on apoptotic cell death induced by etoposide or calcium ionophore. These results indicate that **Bcl-2** and **Bcl-x**(L) protect mitochondria against the loss of function during both **apoptosis** and at least some forms of necrotic cell death. The ICE family proteases act at a different step other than the loss of mitochondrial membrane potential.

L22 ANSWER 46 OF 47 MEDLINE on STN
ACCESSION NUMBER: 96380907 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8788920
TITLE: 1-methyl-4-phenyl-pyridinium ion (MPP+) causes DNA fragmentation and increases the **Bcl-2** expression in human neuroblastoma, SH-SY5Y cells, through different mechanisms.
AUTHOR: Itano Y; Nomura Y
CORPORATE SOURCE: Department of Pharmacology, Hokkaido University, Sapporo, Japan.
SOURCE: Brain research, (1995 Dec 18) 704 (2) 240-45.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961031
AB **Apoptosis** has been shown to be induced by some pathological stimuli. MPP+ is a neurotoxin and an inducer of parkinsonism. When SH-SY5Y cells, human neuroblastoma cell line, were treated with MPP+, cell death estimated by lactate dehydrogenase (LDH) leakage assay occurred. The cell death was associated with the DNA fragmentation into nucleosomal fragments at 180 bp, suggesting that MPP(+)-induced cell death of SH-SY5Y cells occurs through **apoptosis**. Although SH-SY5Y cells natively express **Bcl-2** protein, which inhibits **apoptosis**, the level of **Bcl-2** protein in SH-SY5Y cells increased with increases in the treatment periods of MPP+. MPP+ inhibits the mitochondrial respiratory chain. The other inhibitors of the mitochondrial respiratory chain, antimycin A and oligomycin, also caused cell death associated with DNA fragmentation, but did not increase the **Bcl-2** protein level, suggesting that an MPP(+)-induced **apoptosis** may be due to the inhibition of the mitochondrial respiratory chain but the MPP(+)-induced increase in the **Bcl-2** protein level is not due to it. A protein kinase inhibitor, staurosporine, inhibited the MPP(+)-induced increase in the **Bcl-2** protein level, but not the MPP(+)-induced cell death. These results also suggest that the mechanism by which MPP+ increases the **Bcl-2** protein level is different from that of MPP(+)-induced cell death.

L22 ANSWER 47 OF 47 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 94148090 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8313978
TITLE: Mitochondrial respiratory chain inhibitors induce **apoptosis**.
AUTHOR: Wolvetang E J; Johnson K L; Krauer K; Ralph S J; Linnane A W
CORPORATE SOURCE: Department of Biochemistry, Monash University, Clayton, Vic., Australia.
SOURCE: FEBS letters, (1994 Feb 14) 339 (1-2) 40-4.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19940330
Entered Medline: 19940318
AB In this paper the specific mitochondrial respiratory chain inhibitors rotenone and antimycin A and the highly specific mitochondrial ATP-synthase inhibitor oligomycin are shown to induce an apoptotic suicide response in cultured human lymphoblastoid and other mammalian cells within 12-18 h. The mitochondrial inhibitors do not induce **apoptosis** in cells depleted of mitochondrial DNA and thus lacking an intact mitochondrial respiratory chain. **Apoptosis** induced by respiratory chain inhibitors is not inhibited by the presence of **Bcl-2**. We discuss the possible role of mitochondrial induced **apoptosis** in the ageing process and age-associated diseases.

Searched by: Mary Hale 571-272-2507 REM 1D86

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=> s  hockenberry d?/au;s simon j?/au;s s tzung s?/au)
L23           4 FILE MEDLINE
L24          13 FILE BIOSIS
L25           3 FILE EMBASE

TOTAL FOR ALL FILES
L26          20 HOCKENBERRY D?/AU


L27        2289 FILE MEDLINE
L28        2456 FILE BIOSIS
L29        1784 FILE EMBASE

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L30        6529 SIMON J?/AU


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L32          20 FILE BIOSIS
L33          12 FILE EMBASE

TOTAL FOR ALL FILES
L34          45 TZUNG S?/AU

=> s l26 and l30 and l34
L35           0 FILE MEDLINE
L36           0 FILE BIOSIS
L37           0 FILE EMBASE

TOTAL FOR ALL FILES
L38           0 L26 AND L30 AND L34

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